VOL. 16 (NEW SERIES) NO. 2 MAY, 1953

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LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

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Brown, A. B. (1845): *Rev. Neurol.*, 169, 427.

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J. Neurol. Neurosurg. Psychiat., 1953, **16**, 59.

THE PRODROMES TO CORTICAL LOCALIZATION*

BY

PROFESSOR SIR GEOFFREY JEFFERSON

From the Department of Neurosurgery, Manchester Royal Infirmary

This lecture is dedicated to the memory of a man who excelled as greatly in qualities of character, in probity and dignity, as in mind. University College and its hospital has had a major share of great men and we do well to honour them. It would not become me to try afresh a description of Rickman Godlee since entirely admirable accounts have been given by those better equipped with personal knowledge than I. I can do no more than add my respects.

A suitable exercise for this occasion would be the making of a journey back into the past. Its object would be to discover what sort of knowledge Rickman Godlee must have possessed at the time of his famous operation on young Henderson, an event so perfectly described by Wilfred Trotter (1934) that it would be rash to venture it again.

We know that Godlee was a well informed anatomist since he had taught the subject for long in his earlier years. That fact, together with the intimate knowledge of antiseptic principles learned from his famous uncle, fitted him as few men could have been for the bold surgical adventures that he undertook in skull and chest. But though we can be sure that Godlee knew the anatomy of the brain very well, what of its physiology? What could he have been taught or have learned about that? More particularly, by what steps had that knowledge been built up during the nineteenth century? There is much to examine. There is no tract in the cord or brain-stem, no nucleus, no aggregation of cells, no sulcus, no convolution but has a history of its own, a history in all cases still uncompleted. In the present conspectus it will be difficult to make more than a regrettably cursory survey of much fascinating material, of discoveries by men famous in their day and famous still. We shall find confirmation of Frederic Bartlett's (1950) statement that an element of doubt is present in all beliefs, that no man believes what he believes all the time. We shall see doubt increasingly invading neurophysiological thought in the middle of the nineteenth century up to the final revolution that occurred in Godlee's lifetime.

* The Godlee Lecture delivered at University College on October 23, 1952.

Early View on Brain Function

The history of brain function can be arranged in an overlapping pattern, in which anatomy and comparative anatomy, dissection and experiment, fused by degrees with clinical medicine and gross pathology. Many of the experimenters were clinicians and one finds them often in a dilemma in which the facts of bedside observation were at war with deductions drawn from experiment, but as usual the latter were taken as the sounder evidence. They were compelled therefore to propose or adopt theories for neurological events which must have strained their credulity. I shall quote examples later.

It is remarkable that the anatomists were able to form as good a picture as they did of nervous activity by a judicious mixture of common sense with observation and by comparisons between the nervous structure of different animals. The matching of structure with potentialities of behaviour had obvious merits but it was a more difficult task than then appeared and is far from done with yet. The fact that creatures could move, eat, reproduce themselves, fight, and survive with little more than a double thread of nervous tissue and ganglia of various sizes and shapes would suggest strongly that the cerebral hemisphere of the higher species had mental rather than motor properties. There seemed to Herbert Mayo in 1827 to be a " principle of improvement " in the nervous system plain to the eye, and this gave a particular point to the researches in comparative anatomy of Cuvier, Vicq D'Azyr, Arnold, Tiedemann, Newport, Robert Owen, and Carpenter. At the same time dissections of the brain by those men and by Rolando, Charles Bell, Reil, Gall and Spurzheim, Serres, Mayo, and a host of others, led to a useful working plan of the relationship of the hemispheres to the brain-stem and spinal cord. It came to be generally conceded

FIG. 1.—Dissection of pyramid running supposedly to the corpus striatum (Herbert Mayo, 1827).

that in the carnivores and in man the posterior columns of the cord were sensory and the anterior motor, leaving the lateral columns indeterminate. The posterior columns were traced to the thalami and the anterior to the corpora striata. This conclusion was not arrived at without pain for in contemporary engravings the artists failed to make the pyramid end in the corpus striatum as can clearly be seen in Solly's diagram and in Mayo's beautiful dissections (so much admired by Elliot Smith). Bell too speaks of the pyramids as streaming either through or past the striate bodies towards the cortex. To some the apparent continuity of the posterior columns with the cerebellum suggested a sensory function there, but this view was not held by many. Alexander Walker (1834) wrote a long and quarrelsome book in which he contended that the posterior columns were motor and the anterior columns sensory but on the whole at that date the best opinion agreed that the striata and anterior columns were motor, the thalami and posterior columns sensory. As late as 1869 the curious reader will find in Carpenter's *Physiology* (7th edition) a designation of the corpus striatum as the motor ganglion, the optic thalamus as the sensory. Of discrete limb localization there was nothing. It is true that Saucerotte (1778) in his essay presented for the prize offered by the Academie Royale de Chirurgie on contrecoup, concluded that the striata were motor to the hind-limb, the thalami to the fore-limb. This view found experimental confirmation from Serres and Loustan (1826) and clinico-pathological endorsement by Foville and Serres independently. The proposal met with little support in England, but the existence of a theory for the independent cerebral representation of arm and leg indicates clearly the need felt by clinicians for an explanation of the monoplegias. Bouillaud (1830) voiced their unrest.

After Saucerotte's abortive attempt to find a separate localization for limb movements nothing very positive happened for the best part of 100 years. In the meantime the physiologists by experi-

ment crystallized all knowledge into a formula that confirmed anatomical results and was accepted for decades. It was based on the fact that experimental excitation of the brain-stem from the quadrigeminal tubercles downwards as far as and including the spinal cord led to movements, frequently convulsive. The cortex itself was inexcitable and indeed movement was the more easily caused the further the experimenter descended from it along the neuraxis. From Haller (1755) and Lorry (1760) to Legallois, onwards to the best observer of them all, Flourens, and on again to Magendie and everyone else, all were agreed upon this—the brain was unresponsive except at the lower and lowest levels. The hemispheres were the seat of the " will " ; they excited movement by playing on these motor mechanisms. But how they did so no one knew and no nice man would ask ! So we find even as late as 1886 Hughlings Jackson writing, " When I first began the investigation of nervous disease I supposed, as most other physicians then did, as perhaps most still do, the seat of epilepsy to be in the medulla oblongata ". The impressive words here are " as most still do "—so deep was the imprint of the physiological teachings of the past on his contemporaries' minds. Their reluctance to accept evidence that swerved abruptly away from tradition would have amused, and I fear delighted, Wilfred Trotter. Flourens had shown that creatures lacking their hemispheres could still move, swallow, fly, swim, but had lost the will to do so. They lived in a sleep but were denied the privilege of dreaming (so Flourens said). Very soon Bouillaud showed that very similar states resulted from excision of the frontal lobes only : his animals became, he said, " profound idiots ". Many years were to pass before Munk, Goltz, and Ferrier would return to this subject better equipped to analyse it. Imperfect though the earlier experiments were they none the less led to important conclusions such as that loss of the vision in the contralateral eye resulted from hemispherectomy, a disability soon proved to follow injury to the geniculate bodies. Again, Flourens' experiments on the cerebellum settled once and for all its coordinating function. Rolando had been wrong about this, for seeing how extremely weak and clumsy his animals were after wide damage to the cerebellum, weak yet not paralysed, he concluded that the cerebellum's function was " sthenic ". Up to a point this is true but Rolando spoiled it because of his seduction by the sirens' song of the new science of electricity ; he saw the cerebellum as a living voltaic pile energizing the whole brain. Rolando, though a trifle off his course in this, was at least nearer the truth than Magendie who proved to his own entire satisfaction that injury to the cerebellum made the animal run backwards, whereas injuries to both corpora striata made it run forwards as if propelled by an irresistible force.

Looking back over this period, one in which a surprisingly large number of important books on neurophysiology and neurology were written, we see that the experimenters, frustrated by the failure of their crude cerebral stimulations, turned more and more to ablations. We shall see later why their stimulations failed. In the meanwhile we must be content with the general inference that the corpus striatum was first choice as a motor organ. A few writers recorded movement following its stimulation, but as many denied it. One thing was certain, that hemiplegia followed its destruction in man, or so they held.

The Phrenologists

Before proceeding further we must pause for a glance at the phrenologists. Their work from the time of the Napoleonic wars onwards played a most important part in all scientific thinking. The proposition of Dr. Gall, supported by Dr. Spurzheim, that the hemispheres were not functionally univalent but were a mosaic of special properties, mental or emotional, that they were in fact a " plurality of organs ", made an immediate appeal to European thought. The special point to which attention should be drawn today is the excellence by the standards of their time of their huge " *Anatomie du Cerveau* ". They were the first to show that the trigeminal nerve was not lightly implanted in the pons but that its root fibres could be dissected down as far as the inferior olive. Gall in particular was a serious anatomist. He was on the side of the angels in insisting that the study of the brain by horizontal slices, the common dissecting room method then and one too much used by pathologists today, was no way to study that organ intelligently. All dissection must be from the medulla and base upwards. Only thus could any relation between structure and function be discerned. It was an admirable practice. It has its lessons for us today for we have concentrated on the cortex too long. Only in such a way can we see the brain as an integrated organ for the synthesis of experience, as the afferent system that Sherrington from his earliest days insisted that it was.

We can look back on phrenology now with a more tolerant eye. We see it most obviously as the first attempt, though a wrong one, at the functional parcellation of the cortex. But if we read the literature of that time we quickly see that the more

intelligent adherents to the cause, such as the members of the Edinburgh Phrenological Society, made the first important enquiries into applied psychology, especially criminal psychology and into the natural history of delinquency. Their work in those directions has not been properly appreciated. There was so much that was ridiculous, especially their decision that the cerebellum was the seat of sexual urges. But even there they were the forerunners of Freud in making sex a subject proper for discussion. " Why ", wrote Gall, " make use of circumlocution in treating of the most indispensible and powerful of all the instincts ?" Their localization of sex in the cerebellum, though it must have led to as many piquant drawing-room discussions as did Freud's doctrines, proved a major mistake and contributed much to the ultimate discredit of all their theories. Yet years later we may discover Morrant Baker in the 1867 edition of Kirke's " Handbook of Physiology " casting a wistful look back and saying that " even if the system of phrenology might be false, the theory might be true ". However pure the intentions of Gall and Spurzheim when they began, it is manifest that they quickly allowed themselves to be seduced by the curious, the fashionable, and the wealthy, and became little better than charlatans. Their 33 areas with singular properties became objects of scorn.

FIG. 2.—Phrenology's plurality of organs. Area 29 (in orbit) is the centre for language, 23 for colour perception, 32 is wit (Spurzheim).

There is another reason for speaking of phrenology. It is because of its eventual influence on Broca's localization of speech. Bouillaud had become an adherent, if a critical one, to phrenology. He accepted the phrenological localization of language and memory of words in the under surface of the frontal lobes, though, as he said, " Dr. Gall had announced rather than demonstrated " the fact. Bouillaud was the first to express surprise that no neurologist had enquired before 1827 into the location of the pathological lesions present in patients with those verbal difficulties that Trousseau later christened aphasic. " I do not know " he said " why no one has occupied himself with a subject not less interesting in its physiological relation than in its medical ". He was quite right: no one had. The lesions would be found, Bouillaud said, always in the frontal lobes and offered a prize to anyone who could bring contrary evidence. It was never won, or, more accurately, never paid. But so it came about that when Paul Broca published his first specimen from an aphasic subject in 1861, his famous " Tan, Tan ", he hit upon the posterior end of the third frontal convolution, not because it alone was diseased, far from it, but because it was nearest to the phrenologist's subfrontal orbital surface speech areas. The whole story, and a fascinating one it is, has been exquisitely told by Souques (1928). He gives full credit to the prior observations of Marc Dax who, before anyone else, observed that it was the left hemisphere that was usually found damaged in aphasics, a fact that did not dawn on Broca until he had seen Dax's posthumous but unpublished thesis.

Further Experiments

It is time that we returned from these bye-ways to the main road. Although new experiments being made apace they were doing little to disturb the accepted teachings, yet we can discover growing unrest at the discrepancies between theoretical and applied neurophysiology. Let us turn for instance to Longet whose book of 1842 is the most important in the first half of the nineteenth century. He

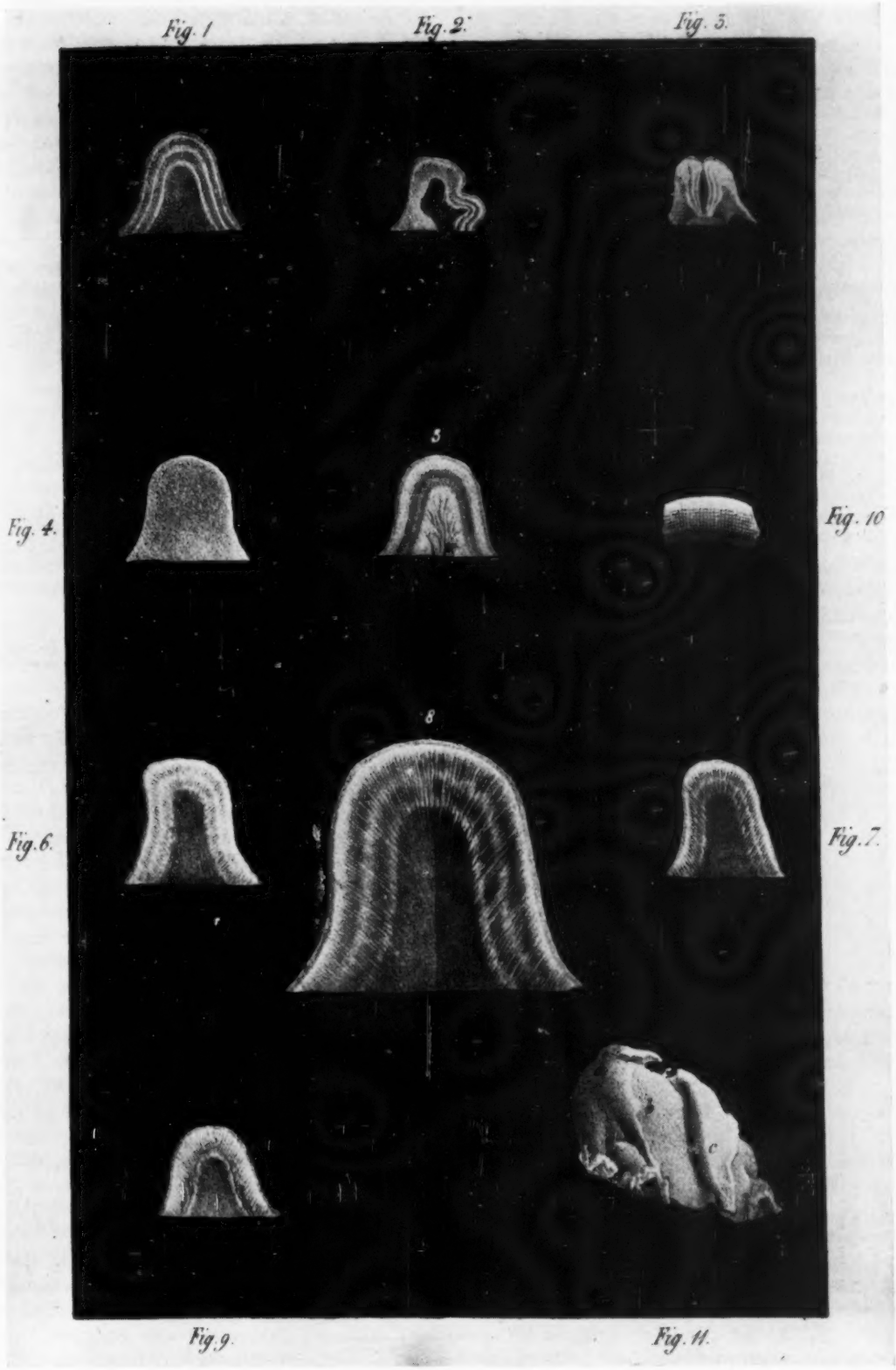

FIG. 3.—Cortical layers in different animals according to Baillarger (1840). The large central section is pig's cortex, with fibres entering grey matter.

reviewed the experimental proofs of himself and others. Of his own he says this :

> " On dogs, rabbits and on some kids we have irritated with a knife the white substance of the cerebral lobes, we have cauterised them with potash, nitric acid etc.; we have run galvanic currents through them in all directions without succeeding in evoking involuntary muscular contractions ; the same negative results were found in directing these agents to either grey or white matter."

Longet goes on to sound a warning note against the too rigid interpretation of these laboratory results. He said :

> " However, the pathologist would fall into a grave error of generalising on what experiment reveals if he deduced that, in partial affections of the cerebral lobes of men, all must follow as in these experiences. Indeed every day in acute and chronic affections of these organs one sees, on the contrary, epileptiform phenomena supervene, partial contractions of the face, of the mouth. . . . To explain the invasion of convulsive phenomena experimental induction leads us to suppose that in men disease can stir in the bosom of the brain irritations such as artificial and immediate stimulation cannot provoke."

Longet's general inference was completely true. Local disease of the brain induced in some way a sort of undefined selective effect on the executive lower levels. Local palsies, for example, caused by fibrous tumours of the meninges, had to be explained by attributing them to counter-pressure on the striate bodies or lower down still, and if the same sorts of lesions caused fits, why, they were due to counter-irritation of the mid-brain or spinal cord. Longet had many important experimental results to record. One of these was that in his own experience he had found the corpora quadrigemina themselves inexcitable but that movements occurred only when one penetrated deeply towards the white matter of the mid-brain. The anterior were stations on the visual pathway.

Mention must now be made of some long forgotten experiments by the King's College neurologist, R. Bentley Todd, whose name lives coupled to the post-epileptic hemi- and mono-plegias that he was the first to describe in detail though they had been studied by Bravais. Todd's work was described in the Lumleian lectures for 1849 on convulsive diseases. He very rightly asked how a spinal or medullary theory of epilepsy could account for those many fits in which loss of consciousness was the only sign. It might have been accounted for on a mesencephalic basis if the opinion of Gerdy (1840) was adopted that this structure was the seat of consciousness. Over 100 years later that theory was to be reborn. But Todd's ideas were not quite those of Gerdy. He proceeded to describe his own experiments on rabbits. He had wished, he said, to ascertain whether galvanic stimulation of the brain (by a " magneto-electric rotation machine ") gave rise to anything similar to the tetanic effects seen by excitation of the spinal cord. Similar but still tetanic contractions were obtainable, he found, from the medulla. His next objectives were the corpora quadrigemina and the mid-brain but in process of exploration he made an observation that has been forgotten, perhaps because Hitzig was unaware of it and Ferrier overlooked it.

> " Having passed fine bradawls into the cranium in such a direction as I had previously satisfied myself would lead to this organ, [the mid-brain] I subjected it to the influence of that machine ; general convulsions were produced of a character essentially different from those which resulted from stimulating the spinal cord and the medulla oblongata. They were combined movements of alternate contraction and relaxation, flexion and extension, affecting the muscles of all the limbs, of the trunk, and of the eyes which rolled about just as in epilepsy. On inserting the awls into the hemispheric lobes still different effects were produced by the application of the machine. I could observe nothing like convulsions but slight convulsive movements of the muscles of the face took place which were no more than what would be caused by the stimulus of galvanism acting upon the nerves of the face.
>
> These experiments, which I repeated several times, and each time with like results, seem to denote that convulsions are modified according to the part of the cerebro-spinal axis which is primarily excited."

Todd goes on to say that stimulation or disease of the spinal cord or medulla would cause tetanus-like or opisthotonic attacks ; of the corpora quadrigemina or the mesencephale they would be epileptic. How modern all this is, though it has been eclipsed by much that was discovered later. Todd refers to experiments by Weber confirmatory of his own. Todd was unable to see anything surprisingly new in these small movements that could be caused by stimulating the hemispheres. His words suggest either that he regarded them as artefacts or more likely that they were not epileptic enough for his purpose. This was a pity since he so clearly had hold of something vitally interesting. The specific mention of electricity by Longet and Todd will only surprise us into the reflection that this method of stimulation had been so little used and then without revelation during the decades since the days of Galvani's (1791) and Volta's (1800) publications.

Nerve Cells and the Cerebral Cortex

So far no mention has been made of the cellular structure of the brain. There was a good reason. None of the neurologists so far considered could see any utilizable linkage between structure and action, except in the broad way that nervous energy very

likely originated in the grey matter, as Willis had believed. It is clear enough to our eyes that had they given more weight, or even their serious attention, to the discoveries that the improved art of microscopy was making they might have found some of the missing clues. Excellent anatomist though Reil was, he had held that the grey matter was only laid on the white without any real continuity. Several authorities were of the same opinion. That the fibres of the white matter could be seen entering the grey was shown conclusively by Baillarger (1840). It is interesting that his monograph, the first devoted to the cortex alone, should have enabled him to have described at once the six-layered cortex that we know today. A white line had already been reported " in the cortex of the posterior convolutions " by Vicq D'Azyr (1786) and by Gennari (1782). Meckel (1817) observed a white lamination in the cornu Ammonis but nowhere else. Only Baillarger saw the six layers as a widespread cortical arrangement. He says nothing about cells ; he saw the cortex, as Willis had done, as a motivator. He recollected Rolando's explanation of the laminated arrangement of the cerebellar folia which had reminded Rolando so strongly of a voltaic pile that he assumed that the cerebellum's function was to energize the brain and to be to that extent motor. Baillarger thought that it was rather the cerebral layers that had this function. He traced white fibres into the cortex and found many running horizontally. We still remember Baillarger and the inner and outer white fibre bands that he was the first to delineate.

Nerve cells themselves had been seen originally in the large ganglia of the mollusc by the French naturalist, Dutrochet (1824), in 1839 by Valentin, by Purkinje (1837), by Ehrenberg (1836), and in increasing detail by Remak, Hannover, Bidder, Stilling, Clarke, Wagner, Todd and Bowman and many others famous in the annals of micro-anatomy. In 1851 both the crossed and the direct pyramidal tracts were accurately located in the cord by Türck of Vienna. Türck's observations were of uncommon merit and can be read with profit to this day. He could not be sure of the precise origin of the pyramidal fibres superiorly. They seemed to come from high up in the brain, maybe from the lenticular nuclei and from the cortex. His experimental cord incisions and clinical deductions made him as sure as he could be that they were motor in function. Nine years later he proved that the sensory pathways ran through the posterior part of the internal capsule.

As for the cerebral convolutions, they had been figured by anatomists for centuries with increasing precision. Names were attached to them only by degrees. For our immediate purpose the most important was the fissure of Rolando. It was actually named by the French anatomist, Leuret (1839), who in his plates of the brain paid more attention than anyone has yet done to the sulci. He had, he said, found a furrow about midway along the brain's convexity and found it very constant in both monkey and man and said, " I have called it the furrow of Rolando ". Rolando had described it eight years before. However, it should have been named after Vicq D'Azyr who had priority over Rolando, but the edition of Vicq

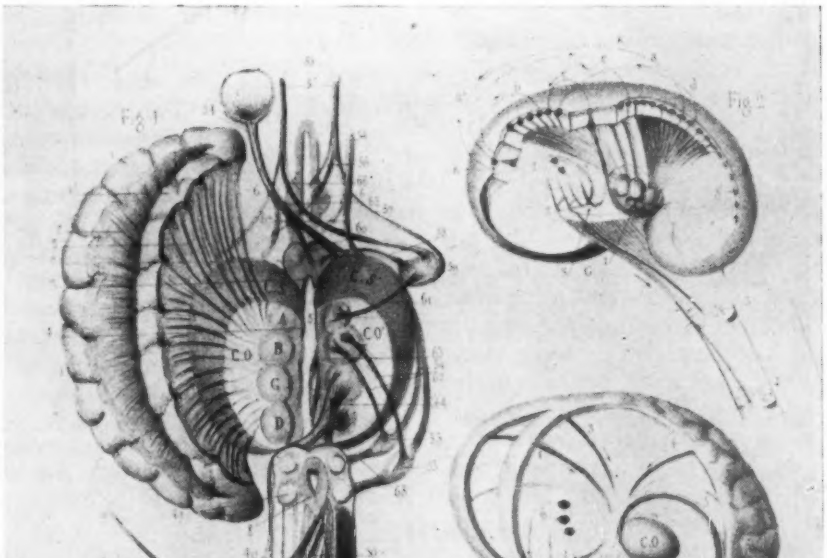

FIG. 4.—Luys' (1865) centres for face, trunk, and leg in the corpus striatum.

D'Azyr's anatomy that Leuret used lacked some of the plates through some fault of editorship (see Broca on this subject, 1878). The fissure was renamed the central sulcus by Huschke in 1854.

It was in front of this furrow that W. Betz, Professor of Anatomy in Kiev, described briefly in 1874 the great pyramidal cells of the fourth cortical layer. Unfortunately he did not illustrate his short paper, the results of which were amply confirmed with excellent figures by Bevan Lewis in 1879. Betz merely gave the average sizes and positions of the cells and described them as having large axis cylinders and large vertically directed dendrites. " Ich möchte sie Reisenpyramidalenzellen nennen " he said. He added that he found them in dogs in just that part of the brain that Fritsch and Hitzig had found excitable four years before. Betz said that they doubtless have motor functions, and that terse statement marks an epoch in neurology. The rest of Betz's paper is given up to the naming of the continuation of the motor area over onto the medial surface of the brain. He proposed the name " lobulus paracentralis " for this, a name that has survived. Betz believed that it, rather than the precentral convolution, was the homologue of the excitable cortex of the dog.

This cursory survey of so much of the greatest importance has not perfectly synchronized with the neurological story of the cortex. It has led us on too far. We must go back to the publication of Luys' researches in 1865, for he had something to say about motor cells that might be overlooked. Luys believed that the corpora striata were the effective motor organs, but he was as badly in need of separate mechanisms for head, arm, and leg as his predecessors. Rather fancifully he assigned them to the different arcades of the corpus striatum and made hard mechanical diagrams to show this functional arrangement. But though he did this he was impressed by the cortical cells. Comparatively large cells he saw in histological sections lying deep in the cortex. They were, he stated, incontestably motor in function. He drew that conclusion from comparison with the anterior horn cells of the spinal cord, which were so much larger than the sensory cells of the posterior horns. On the same grounds he correctly assumed the substantia nigra to be involved somehow in movement. He added that those cells " which seem more particularly devoted to act as the substratum to manifestations of voluntary movement are localised in the deepest layers of the cortical cells ". Does this appear to be a contradiction—motor cells in the cortex, discrete motor centres in the striatum? Not by any means. Luys proceeded to say that there exists in the cortex distinct localizations whence the corpus striatum draws its exciting principle, but he could not define them topographically. He may well have had in mind the precentral gyrus because he described its local atrophy in patients with old-standing amputations.

The difference, then, between what was believed before and after 1870 is a matter of where the localization of discrete function lay, whether in basal ganglia or in the cortex. We can see already in Luys' work that invocation of the cortex that was the hall-mark of Hughlings Jackson's work. And we shall do well to recollect that even after Ferrier had fully established the existence of motor centres in the cortex for all manner of small movements, there were many who thought that the motor paths ended in the corpus striatum. For instance, in Dodd's vast review in 1878 of the whole subject up to date, there is a diagram showing the efferents from the excitable cortex ending in the corpus striatum. It may be objected that others surely thought that the cortical efferents ran down into the cord. Certainly, they did. But no great number of observers or research workers ever believe exactly the same things. It would be dull if they did and progress would be slower. As for Luys, it was in the same interesting volume that he described the nucleus that has since borne his name.

Jackson, Hitzig, and Ferrier

The stage is now set for the entrance of the last three figures—Hughlings Jackson, Eduard Hitzig, David Ferrier—who lead us to Sir Rickman Godlee. Jackson's superb contribution was based on induction from the experimental material provided by people with epilepsy. Between 1861 and 1870 he had concentrated his attention on local fits, convinced as he was that the simpler the epilepsy the more profitably it might be studied. He once wrote :

> " I am fully aware that there are admirable accounts of the worst fits as types, but some of the accounts are descriptions more of dramas of great human interest than calm and coldly scientific observations in an orderly sequel of the outward phenomena of an inwardly suffering nervous system."

He brought his views to a focus in his famous papers, " A Study of Convulsions " (1870), followed by two more of equal importance in 1873 and 1875. His observations and his conclusions are so well known and have been commented upon and expanded with such masterly penetration by F. M. R. Walshe that I need refer only to those most relevant to our immediate purpose. Jackson from the beginning was convinced that there was a " dis-

charging lesion" in local fits, and that they were caused by damaged nerve cells. The alteration that made them liable to explosive discharge was, he thought, of a chemical character.

As for the part of the brain involved, Hughlings Jackson originally believed that it was the "region of the corpus striatum" or the convolutions near to it. He says "The loose term 'region of the corpus striatum' is used" and a few lines later he adds:

> "As the convolutions are rich in grey matter I suppose them to be to blame, in severe convulsions at all events; but as the corpus striatum also contains much grey matter I cannot deny that it may be sometimes the part to blame in slighter convulsions. Indeed, if the discharge does begin in the convolutions, no doubt the grey matter and lower motor centres, even if these centres be healthy, will be discharged secondarily by the violent impulse received from the primary discharge."

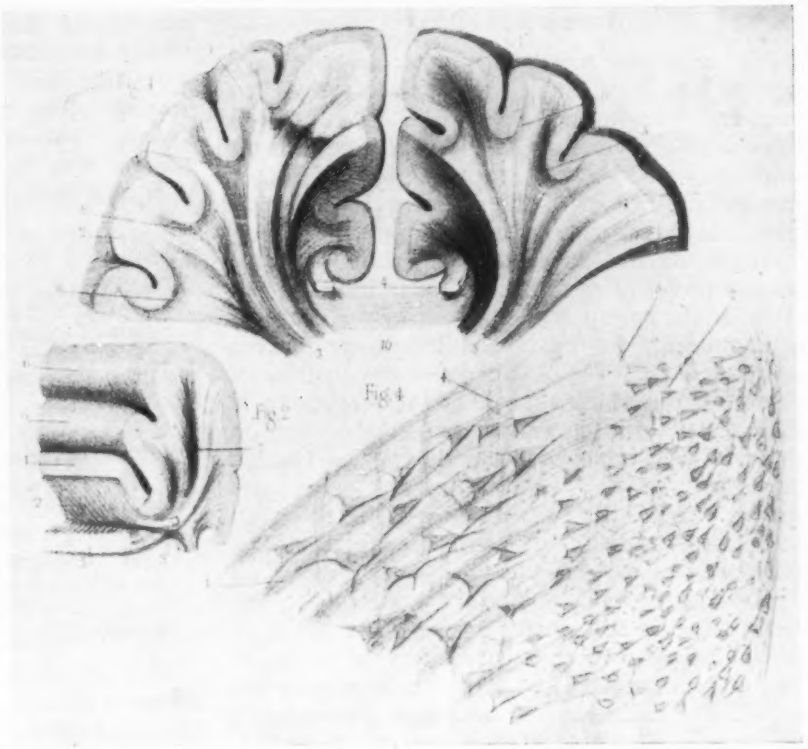

FIG. 5.—The large pyramidal cells in deeper layers of cortex that Luys (1865) thought were motor.

This of course is true. It would not be unfair to say that Hughlings Jackson had arrived at the cortex as able to produce movements, if convulsive ones, before the physiologists and that only respect for their laboratory findings caused him to express himself in such guarded language. Years later when the excitability of the cortex had been fully established he made no secret of his original attribution of local fits to the corpus striatum and the neighbouring convolutions. Addison had said that fits without loss of consciousness usually meant that a gross cerebral lesion, such as a tumour, was present. This was a wise clinical generalization and Jackson agreed with it but in his acceptance he showed the particular quality of his genius. He was not so much interested in the tumour as in the evidence that such examples presented of local instability in the neighbouring damaged nerve cells. That this was an enormous advance in neurology is very clear.

In Hughlings Jackson's day the most powerfully explosive substances were nitrogenous, e.g., nitroglycerine; he suggested that the nitrogenous substances in nerve cells might become altered if they were diseased into unstable compounds and assume "explosive" qualities in a physiological sense. Just so today Russell Myers (1951), for instance, uses a modern physical description when he refers to this explosive instability in a different way saying that "epileptogenic focus" may be envisaged as a cortical site of biophysical and biochemical alterations of cell-membrane permeability and cellular respiration leading to depolarization of the neurons. The two statements so many years apart are expressions of probability in the light of existing physical knowledge. Neurology had travelled far since the days when Bravais (with whose name Jackson's is usually somewhat undiscriminatingly coupled by the French) had written his monograph on unilateral epilepsy (1827) without seeing in it the disclosures that Jackson found. I have discussed the subject of Bravais on a previous occasion (1935). Local fits, as we have seen, could not in any way be regarded as something newly observed in medicine. It was the new interpretations by Jackson that were everything. It would be only too easy to diverge into a lengthy discussion on Hughlings Jackson who deserves so much. From this time onwards epilepsy could not be, as he put it, "a proper name" but a state in which each example must be regarded as demonstrating some or other of the physiological properties of the brain.

Fritsch and Hitzig

We come now to the paper that revolutionized cortical neurophysiology. It appeared in Reichert and Du Bois-Reymond's *Archiv für Anatomie, Physiologie und wissenschaftliche Medizin* and was the work of two 32-year-old *privatdocents* in Berlin. It was dated April 28, 1870. Eduard Hitzig wrote several more papers on neurological matters during his life but did not collaborate again with Fritsch. He became professor at the Nervenklinik in Halle, and reviewed the controversies aroused by the doctrines of localization in the second Hughlings Jackson Lecture (1900). The differences in the qualities of Hitzig's and Jackson's minds are very apparent in this address. Fritsch was a zoologist who wrote on electrical fish, amongst other things. In Hitzig's important book "Untersuchungen ueber das Gehirn" (1874) the 1870 paper is reprinted in full with minor alterations. The idea of testing the excitability of the cortex once again in spite of all the failures that had gone before was Hitzig's. He had run galvanic currents through the heads of human beings and seen movements of the eyes. This had encouraged him to try the animal cortex anew. The success of the attempt is known to all the world. The authors attribute the failure of their predecessors to several causes. The loss of excitability which they observed when there had been heavy blood loss in the operative approach would be one important reason. Another and fundamental reason was that the excitable part of the carnivore's brain lay so far forward that it might easily have been missed and no doubt often had been. They suggest that operators had paid too much attention to the posterior parts of the brain because the shape of the skull made that part more inviting for the trephine. In their own early experiments they took away half the skull, but finding the excitable region so circumscribed, they were able later to expose it through a trephine opening. They summed up their own success by saying, "The method is everything". Their conclusions may be summarized as follows, largely in their own words :

(1) "One part of the convexity of the hemisphere of the dog is motor, another part is not motor."

(2) "The motor part lies, generally expressed, more forwards, the non-motor lies more posteriorly. By means of electrical stimulation of the motor part one gets combined muscle contractions of the opposite half of the body."

(3) "These muscle contractions allow themselves to be localised by the use of quite weak currents to defined, circumscribed muscle groups."

(4) "The regions responsive to stimulation were very constant in dogs as verified by the greatest response from the weakest currents."

(5) "The fact is securely founded that a considerable part of the nerve masses of the hemisphere, one can say about a half, stands in relationship to muscle movement."

This is surely an over-estimate. The other, posterior part, was probably the birthplace of the will to move. Their conclusions on the motor function of the anterior half of the brain confirmed the predictions of Meynert (1867) based on dissection and histology.

In their once frequently reprinted figure they marked the centres for neck, fore, and hind limb. The stimuli used were single shocks from a galvanic apparatus. Induced currents they thought were not so reliable because of spread and later Hitzig attacked Ferrier's researches on this ground. Extirpation of the fore and hind limb areas led to weakness of the expected limb. Because of the well established belief in the corpus striatum as a centre for movement we might expect Fritsch and Hitzig to have something to say on that rival apparatus. They investigated its claims by sinking insulated needles into the brain and applying the galvanic current to their butts. Twitchings only occurred when the needle point was so deeply sunk as to be, they estimated, in the region of the cerebral peduncle. (This observation will recall Todd's report.) The contractions were quite unlike those obtained from the cortex, requiring much stronger currents and affecting many more muscles in a convulsive sort of way. They concluded that the subcortical areas played no part in the cortical stimulatory effects that they had seen, for if they had, the muscle twitches should have become more easy to produce the deeper the electrode penetrated. The reverse was the case.

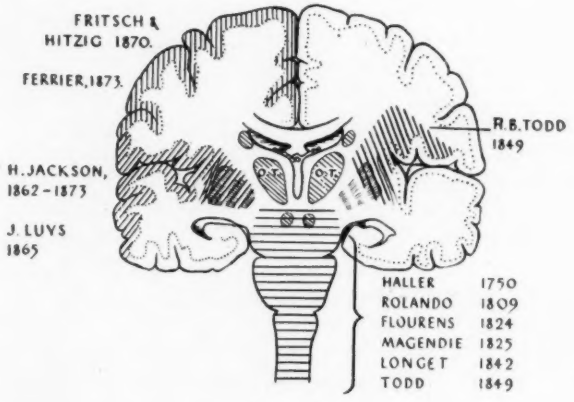

FIG. 6.—Diagram of centres for movement and especially epilepsy.

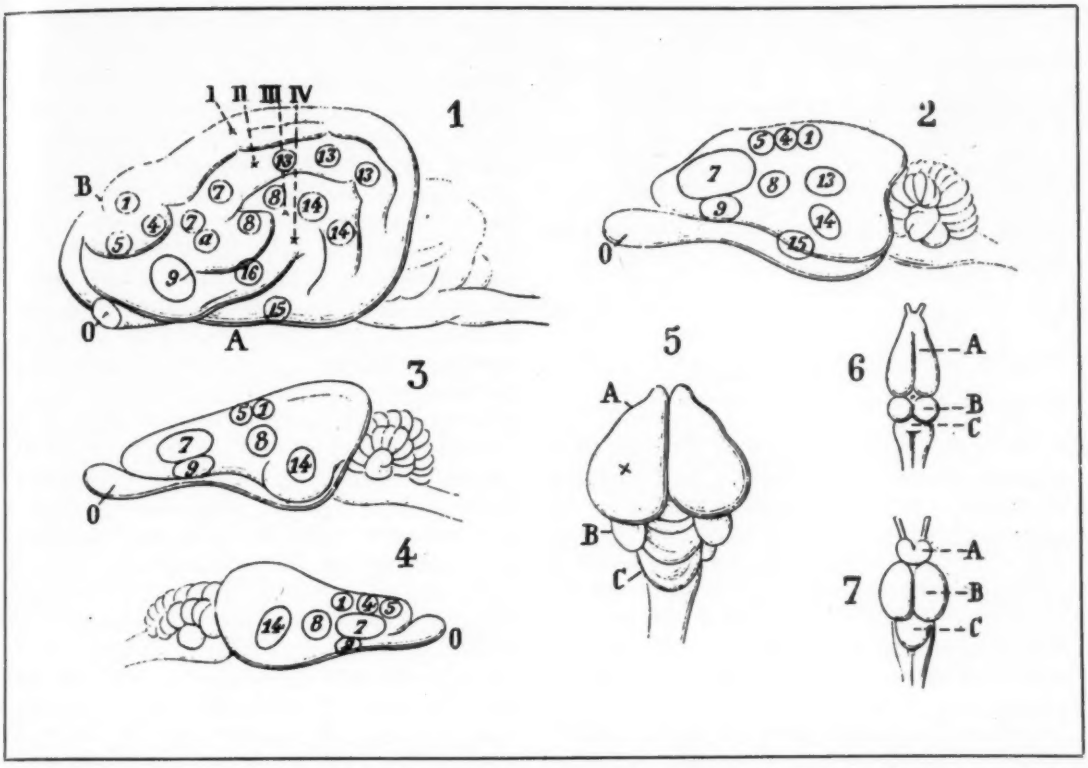

FIG. 7.—Diagram of excitable motor points: 1, dog; 2, rabbit; 3, guinea-pig; 4, rat; 5, pigeon; 6, frog; 7, carp (Ferrier).

In 1873 Hitzig, who from then on published alone, described further researches in the dog, adding more details, and in 1874 he demonstrated the excitability of the monkey's cortex and in the same year did an important piece of work in the identification of the physiological equivalents of the excitable convolutions in dogs, monkeys, and men.

David Ferrier's experiments were first published in 1873 and are so well known that they require little special description. Both he and Hitzig used minimal currents, just strong enough to be felt on the tongue, the one faradic the other galvanic. From the first Ferrier's observations were vastly more detailed and informative than those of Hitzig. One cannot but admire the energy, persistence, and success of that young man on his excursion into a field where so many had failed. As we have seen, nothing short of a very gross movement or even of a convulsion had satisfied the earlier research workers. Hitzig's and Ferrier's evidence was of a much finer quality. It must have been singularly interesting to see a twitch of an eyelid, a slight elevation of the angle of the mouth, a flick of an ear, a clutching movement of a paw, and the protrusion of the claws produced by weak electrical stimulation of the cortex with the electrodes only a millimetre or so apart.

In 1875 Ferrier, like Hitzig, moved onto the monkey's cortex and from that day forwards the exploration of the brain surface became almost a British preserve. Burdon-Sanderson, Victor Horsley, Beevor, Schaefer, Yeo continued to parallel Ferrier's work, until they were joined by the master of them all, Sherrington. So it came that the flood that Fritsch and Hitzig had let loose submerged their discovery without in any way detracting from its merits, which remain secure for all time. Ferrier, it must be added, contributed something that helps us to understand better the failures of the ardent and intelligent workers of the earlier decades of the nineteenth century. The explanation arose out of his use of comparative physiology, a variant on the comparative anatomy of his forerunners. It will be remembered that many of Flourens' most telling experiments had been done on birds. Ferrier showed that the brains of birds, frogs, and fish were difficult to stimulate, often gave no replies and, when they did so, never in form of local movement. These results solved a puzzle. Added to the causes of cortical inhibition already mentioned they gave us a comprehensive answer to a worrying question.

It must not be supposed that the new discoveries

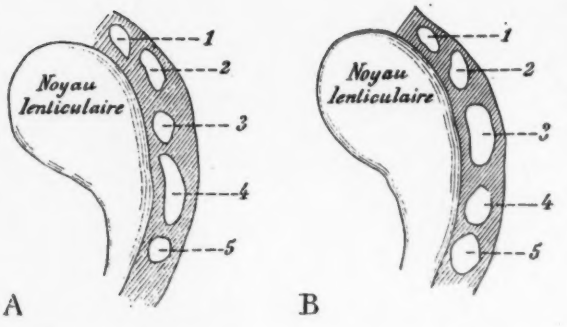

FIG. 8.—Excitable points in internal capsule (François-Franck and Pitres).

which destroyed the long cherished concept of a physiologically homogeneous cortex were accepted without demur. Much prejudice remained to be overcome. Hughlings Jackson writing as late as 1886 said : " When I first began the investigation of nervous disease I supposed, as most other physicians then did, and as perhaps most still do, the seat of epilepsy to be in the medulla oblongata ". The impressive things are the words " as most still do " and the year, 1886. These men would remember the publication in 1859 by the New Sydenham Society of a translation of Schroeder van der Kolk's book " On the minute structure and functions of the spinal cord and medulla oblongata and on the proximate cause and rational treatment of epilepsy ". In this it was made clear that a state of exalted sensibility in the medulla made it liable to discharge by the operation of causes either organic or psychological. They might even recollect the impressive writings of Marshall Hall " On the neck as a medical region " (1850) in which he proved (he thought) that medullary reflexes led to closure of the glottis and that it was cerebral congestion that excited a fit. Tracheotomy was the rational answer and it was applied. Time would be needed to break down the barriers erected by doctrines such as these, doctrines which, though they had not brought complete conviction, were at least in line with the thinking and experimentation of the previous decades. It took time to persuade the critics that the electrical excitability of the cortex was an inherent quality of its own. Some bodies, such as one in New York, set up a committee containing two professors of physiology to make new experiments to test the disturbing new theory. They reported favourably. Putnam followed in Boston (1874) with a similar concurrence, as did Luciani and Tamburini (1878). But many said that the movements were due to the spread of currents into the deeper central nuclei. They were encouraged by Burdon-Sanderson's discovery that the white matter subjacent to the motor strip could be made to give very similar motor replies to faradism. But this was a shortlived check because very soon François-Franck and Pitres repeated the experiments and by brilliant timing were able to show that there was a delay after stimulating the grey matter which disappeared when the white alone was stimulated. François-Franck became in fact a European champion of the new physiology. Not only did he map the arrangements of the motor fibres in the internal capsule, but he and his school demonstrated autonomic visceral results such as changes in pulse rate, blood pressure, and respiration. It was to be expected that the French school would turn their eyes to the visceral effects of cortical stimulation since they had been revivified by that master physiologist, Claude Bernard, and in Marey they had a man who had invented new tools, the tambour and the smoked drum, permitting more accurate analysis. Bochefontaine (1876) saw salivation, rise of blood pressure, contractions of the intestines, bladder, and Fallopian tubes, on stimulating the sigmoid gyrus of the dog. His observations received little credence until the hypothalamus and visceral brain were born in our own lifetime. How right Ferrier was when he wrote (1886) " there is no reason to suppose that one part of the brain is excitable and another not. The question is how the stimulation manifests itself ". Many years were to pass before the truth of this could be more amply confirmed by neuronography, by electronic recording systems, and by looking for results not in the skeletal musculature but in autonomic reactions. These men of long ago had had something to say even there.

The Localization of Tumours

I have been concerned with the anatomy and physiology of brain function and have been forced to omit the running commentary on the manifestations of cerebral pathology that might have been expected. We can imagine that although the cortical localization of movements, of sensation, of vision and the special senses must have been very interesting to everybody, the wider appeal would be made by two other things First that different forms of epilepsy began to have a meaning that they had lacked and, second, that quite superficial injuries to the brain, as Nothnagel showed, caused paralysis or numbness or hemianopia. Surely these facts must have deeply impressed all men. Certainly no less did the demonstration by Roberts Bartholow (1874) in Cincinnati and by Sciamanna (1882) in Rome that movement or convulsions could be caused in man by stimulation of the brain. They

pushed needles through holes in the skull, holes made in one case by an epithelioma, in the other by injury. At the time of Godlee's famous operation there was already in existence a considerable body of convincing evidence that gross cerebral lesions could be accurately localized in the brain. Hitzig himself published (1874) a beautiful case of subacute brain abscess in a French soldier wounded at the battle of Sedan which had given its site away by localized fits and aphasia. The difference between this observation and Macewen's very similar one in 1876 was that the latter had strongly urged operation. A thoroughly convincing series of cases was collected by Ferrier in his book "The Localization of Cerebral Disease" (1878); he included Hughlings Jackson's cases.

The student of this epoch can feel the pressure rising: the time was ripe for surgery. What, we may ask, were they waiting for? Perhaps fear of the consequences of inflicting operative injury on the human brain? The experimenters had not had much success in keeping the larger animals alive after ablation of brain tissue until Ferrier arrived. Then there was the very real danger of infection and this did in fact carry off Godlee's patient eventually but not before the real point of his operation had been proved. Both Bartholow's and Sciamanna's patients had died of intracranial suppuration a few days after the stimulating electrodes had been pushed into their brains. Although the patients already had infected fungi there had been outspoken criticism of such experiments on men. It must have required great resolution to face the storm that would break if a brain tumour that gave no sign of its presence by local swelling of the skull bones was looked for and not found, or if the patient died immediately. By great good fortune, in the last quarter of the nineteenth century, the correctness of Lister's views were being vindicated. The dangers of infection, though present even now, were diminishing. Macewen was the first to move, using the new physiology in the practical treatment of brain abscess, injury, and dural tumours. Lister had been Macewen's early teacher; he was Rickman Godlee's uncle. Lister had apt pupils in these two. Evidently all that was needed now was knowledge, a full sense of responsibility, and courage. Fortunately for us Godlee possessed these qualities in high degree as he stepped over the threshold into a future unknown—but how rich in fulfilment!

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STUDIES IN TRAUMATIC EPILEPSY

2.* FOCAL MOTOR AND SOMATIC SENSORY FITS: A STUDY OF 85 CASES

BY

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General Features of Initial Motor and Sensory Attacks and Their Course
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- Tonic and Adversive Attacks
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Spread of Initial Attack
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Discussion

Summary

When both focal and generalized epileptic attacks occur in the same patient it is not uncommon for the content of the focal attack to occur also as an aura to the generalized seizure. This probably indicates that in each case the site of initial cortical discharge is the same, but that it remains localized in one and spreads widely in the other to involve sub-cortical centres which seem to play an essential part in the spread of the epileptic process. For this reason we here consider together isolated focal fits and the localized aura to major seizures, an "aura" being taken to mean any abnormal motor or sensory change which precedes the loss or clouding of consciousness of a fit and which the patient remembers clearly and can subsequently describe. A focal fit may affect almost any of the bodily functions or sensations, and indeed may affect more than one of these during a single attack. The present study is concerned with those fits which involve the motor and somatic sensory functions. These form by far the largest group of focal epilepsies. Of the 360 cases of post-traumatic epilepsy in this series, over 110 have had one or more epileptic attacks of the type which falls into this group; 85 of these are considered in this paper. The variety of pattern which these cases exhibit is so great that it seems desirable to describe briefly the features of a considerable number of cases. Classification is difficult, and though many types of fit are described, this collection of cases does not by any means cover all the possible varieties which may occur.

The majority of focal motor attacks have both a tonic and clonic element. In the upper limb, for instance, the common pattern is of clonic jerking of the fingers with tonic flexion of the hand and forearm, the whole limb often being drawn up towards the face. Clonic movements may also occur in the contractions of forearm and arm muscles, which are initially tonic. Pure tonic or clonic fits are relatively uncommon, but the beginning of movement in an attack may be either tonic or clonic, and it is often possible to establish the initial type of movement for a given case. Examples of "pure" tonic attacks are seen in the so-called adversive fit when this remains localized (see case no. 31*), while *epilepsia partialis continua* often consists of a "pure" clonic movement. In some ways the pattern of the common tonic-clonic focal

* Part 1 appeared on p. 93, Vol. 15, 1952.

*Except where otherwise stated case numbers refer to those in Table IX. Cases described also in the text are marked "T" in Table IX.

fit suggests that tonic contraction is the presenting abnormality which is interrupted repeatedly by sudden momentary inhibition to cause the clonic element, and as is shown later, an attack often changes from tonic to clonic, but rarely from clonic to tonic during the aura phase. This change is well seen in those cases where tonic spasm initiates the attack but is rapidly followed by clonic beats at first of considerable frequency, but gradually slowing, as each inhibitory interval with relaxation of muscles becomes longer, till the limb falls in a flaccid state and the fit is over. On the other hand in some cases of *epilepsia partialis continua* a rhythmic twitching may occur sometimes of a single muscle or part of a muscle which is continued for hours or days, and in which there appears to be no background of tonic spasm. The impression here is of rhythmic discharge rather than of intermittent inhibition, but of course the short duration of each twitch might possibly depend on sudden inhibition.

A study such as this may not only describe the various forms of aura and focal fit and the relative frequencies with which they occur : it may also attempt to correlate the type of aura with the site of wounding and the neurological deficit shown on clinical examination. Of special interest in this series is the information available with regard to the transition of one type of aura to another, or to a major convulsion, or to some mechanism which arrests the fit. The physiological basis for epileptic phenomena is still largely unknown, but, as will be mentioned later, the circumstances under which a focal fit ceases should not be neglected, as this may be just as much a positive physiological process as the spread from one part of the cortex to another. The latent interval between injury and the onset of fits is also of interest as is evident from Table VII.

TABLE VII

INTERVAL AFTER WOUNDING OF FIRST FIT IN CASES WITH FOCAL CLONIC FITS WITH AND WITHOUT PERMANENT SEVERE HEMIPLEGIA

Time after Wounding of Onset of Focal Clonic Fits	Cases with Permanent Major Hemiplegia	Cases without Major Hemiplegia	Total
0– 1 month	1 (1)*	13 (5)*	14 (6)*
1– 6 ,,	8	7	15
6–12 ,,	5	4	9
1–2 years	3	2	5
Over 2 years	—	1	1
Not known	3	5	8
Total	20	32	52

* The figures in parentheses give the number of cases which had focal fits within a month of wounding but not later (5 year follow-up).

It must of course be emphasized that the information analysed in this study, based chiefly on the careful questioning of patients and their relatives, cannot always be accurate. It is to be hoped, however, that errors due to such inaccuracies will be more than offset by the number of reliable case records available.

In describing our observations we consider first the general features of the common motor and sensory attacks, then note the ways in which the initial discharge spreads in relation both to the body and the cortex, and the ways in which it may cease, then return to a more detailed review of the content of some of the focal attacks. Finally we consider briefly the evidence for the cortical site of discharge of the various forms of attack.

GENERAL FEATURES OF INITIAL MOTOR AND SENSORY ATTACKS AND THEIR SUBSEQUENT COURSE

The material from which we have drawn our conclusions is presented briefly in Table IX, where particulars are given of the patterns of fit reported in each case and also a rough indication of the permanent paralysis, sensory loss, or field defect caused by the wound. Table IX also gives tracings of the skull radiographs for nearly all cases.

Clonic Attacks

On the motor side, the clonic attacks (Table VIII) are sometimes highly localized in origin, as in those

TABLE VIII

PARTS OF THE BODY TO WHICH VARIOUS FORMS OF PRESENTING AURA ARE REFERRED

	Motor Clonic	Motor Tonic	Adversive Tonic	Motor Inhibitory	Sensory Positive	Sensory Negative Numbness and Agnosia	Totals*
Face	11	3	—	—	4	2	20
Head and eyes	4	1	12	—	2	1	20
Thumb ..	2	—	—	—	—	—	2
Fingers ..	3	—	—	—	4	1	8
Hand	10	3	—	4	9	5	31
Arm	11	5	—	1	8	3	28
Abdomen ..	1	1	—	—	—	1	3
Leg	5	1	—	2	2	1	11
Foot	4	—	—	—	2	—	6
Whole side ..	2	—	—	—	1	3	6
Total ..	53	14	12	7	32	17	135

* All *attacks* with differing onset are here recorded, so that one case may be represented more than once.

starting in thumb, index finger, or face, and the movement usually spreads to some extent, but it may remain relatively localized for long periods. The following cases illustrate these varieties of clonic aura :—

CASE 16. **Clonic Aura with Very Focal Onset and Sensory Aura to Grand Mal**

A right anterior parietal brain wound caused at the moment of wounding a well formed visual hallucination " like a playing card all lit up ". Soon after, there was a slight spastic weakness of the left hand. Passive movement sense was reduced and stereognosis was largely absent in the left hand. Pin-prick was poorly localized and appreciation was delayed in the hand and arm. There were no motor or sensory changes in the leg. Some years later, some reduction of passive movement and two-point touch in the left thumb and index were the only abnormalities.

Fits.—**1.** Sudden clonic jerking of the left thumb, then the whole left arm showed tonic stiffening, with fingers extended at the wrist and the elbow flexed : then clonic jerkings of the whole forearm occurred, consciousness was lost, and generalized tonic stiffening with opisthotonos was followed by generalized clonic movements.

2. Sudden numbness of the left hand and forearm was immediately followed by tonic flexion of the fingers and wrist, then clonic movements of these but nothing further, and no loss of consciousness.

CASE 4. **Very Localized Clonic Fits and Generalized Convulsions**

A right Rolandic brain wound soon after wounding caused left hemiparesis and agnosia for the left arm together with complete loss of all types of sensation. Sensation was also reduced in the left leg, but here pain was appreciated as an intense and radiating sensation. Some years later there was slight weakness with increased tone in the left arm. The appreciation of two-point touch and passive movement was reduced, stereognosis was impaired and pin-prick appreciation changed in the left upper limb.

Fits.—**1.** Occasional clonic twitching occurred of the left side of the mouth.

2. The left hand, then the left face twitched, and then felt hot.

3. A sudden feeling of faintness was followed by loss of consciousness, and onlookers describe reddening of the face with generalized stiffening of the whole body followed by clonic movements.

CASE 79. **Partial Continuous Epilepsy of Hand**

A right posterior parietal brain wound soon after wounding caused a severe flaccid left hemiplegia. All forms of sensation were lost in the upper limb for which there was an agnosia, but pain was occasionally appreciated in the leg. There was left homonymous hemianopia. Some years after there was a left spastic hemiparesis more marked in the arm than in the leg, with athetotic movements of the hand. Two-point discrimination was lost throughout the left side, including the face. Localization of touch was very poor in the arm and leg, less so in the face. Stereognosis was abolished in the left hand. Pin-prick sensation was diminished, and hot and cold were not distinguished on the left face, arm, and leg. Dense left hemianopia was present.

Fits.—Fits occurred only early after wounding. There was a constant rhythmic clonic movement of the left hand and forearm. This was a flexion-extension movement with slight supination accompanying the flexion. Tone was increased in all muscles, but there was no tonic contraction of flexion or extension behind the clonic movement. This persisted for 10 to 12 days. The movements then became confined to the left index finger and continued thus for a further three days. It was an active rhythmic contraction of the extensor indices with a slow return to the slightly flexed position of rest. At each movement a flicker of extensor muscle contraction could be seen and felt at the rate of about one per second.

Tonic and Adversive Attacks

Tonic or adversive auras tend to involve major groups of muscles in such a way as to cause strong postural reactions such as turning of the head and eyes or flexion at the elbow with abduction at the shoulder, though rarely it may be more confined while retaining its tonic character. The head, eyes, and upper limb are commonly involved first in tonic fits.

CASE 35. **Adversive Movements as Aura to Loss of Consciousness**

A left frontal to parietal brain wound soon after wounding caused a marked motor dysphasia and right hemiparesis. There was sensory loss of all types in the right hand, but passive movement sense was more severely impaired than appreciation of pin-prick. These changes were less marked in the leg. Some years later there was slight dysphasia and slight weakness of the arm and leg with some increase in tone. There was impaired two-point touch and passive movement sense and also some change in appreciation of pin-prick more in the arm than in the leg. The right hand showed astereognosis.

Fits.—The head was forcibly turned to the right, then the right arm, wrist, and elbow were slowly flexed and bent up towards the head. There was some jerking of the leg, first in the foot, then in the knee, without any tonic element. Then consciousness was lost, but no further movements were recorded. After the attacks there was paralysis of the right arm and leg for some 20 minutes.

CASE 65. **Focal Tonic Fits Affecting One Muscle Only and Generalized Convulsion with Aura of Tonic Stiffening**

A severe and deep left fronto-parietal brain wound soon after wounding caused right hemiplegia and right hemianopia and aphasia. Some years later right hemiparesis persisted. Sensory testing was difficult owing to dysphasia and lack of cooperation, but pin-prick was

TABLE IX.—SUMMARY OF PERMANENT SENSORI-MOTOR

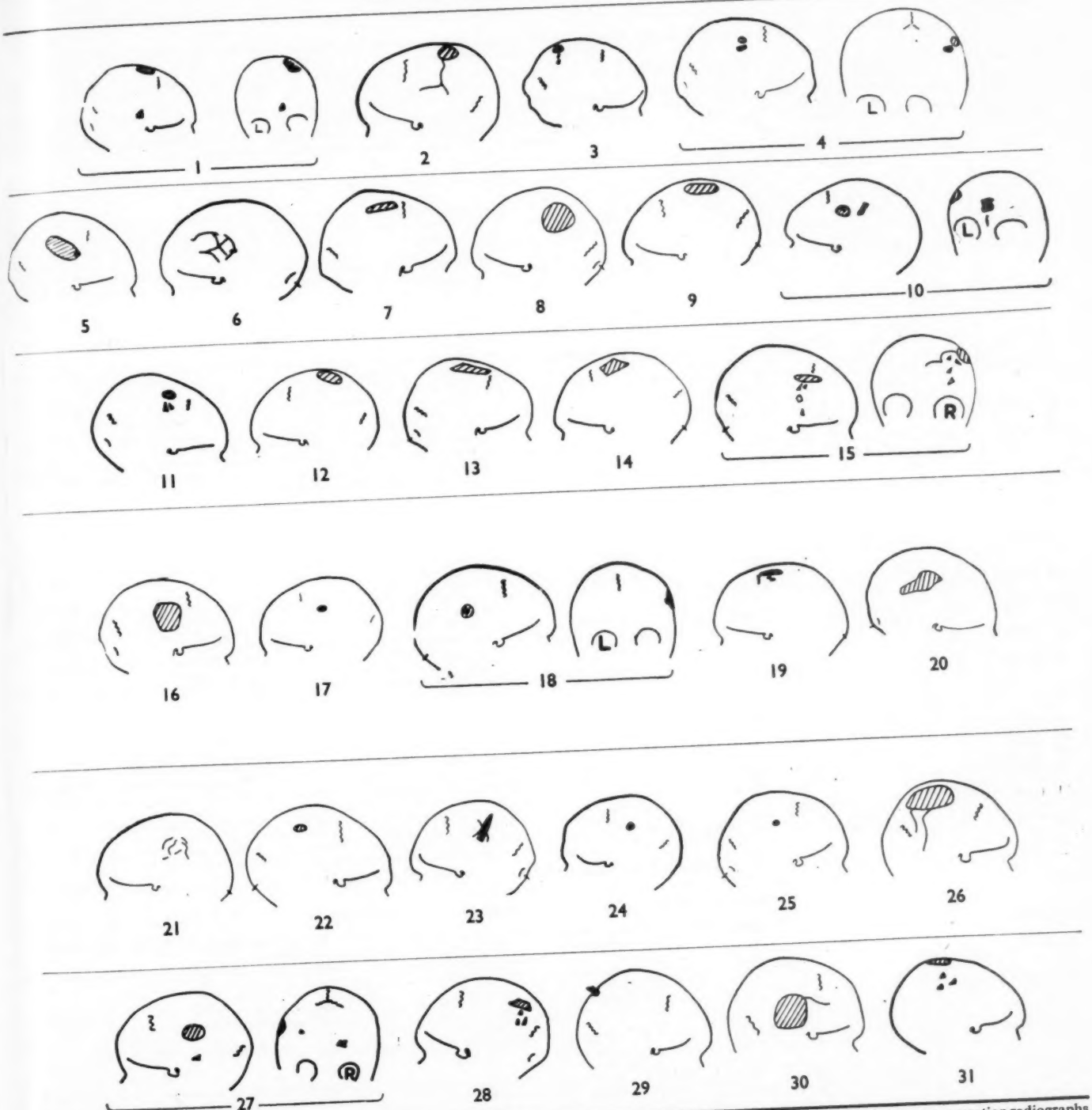
Case and Index Nos.	Side	Motor Loss	Cortical Sensory Loss	Other	Type of Fit
GROUP 1.—*Wounds in the Rolandic region causing limited motor (and often also sensory) loss*					
1 (162)	R.	L. arm, moderate	L. arm, slight	—	L. hand tonic→ L. face clonic→ loss of consciousness†→ general tonic (clonic L. side only)
2 (2789)	L.	R. leg, severe	Nil	—	(1) Tingling R. arm→ R. face→ aphasia. (2) Sudden loss of balance
3 (328)	R.	L. arm, L. leg, slight	L. fingers, slight	L. spatial disorientation	(1) Tingling L. hand, L. arm. (2) Numbness L. fingers→ L. arm→ L. leg→ clonic L. hand→ L. foot. (3) Dizzy→ loss of consciousness, pale, no movements. (4) Tonic and numbness L. abdomen→ clonic L. abdomen
4 (404)	R.	L. arm, slight	L. arm, slight	—	(1) L. face clonic. (2) Clonic L. hand→ L. face→ heat L. hand, L. face. (3) Faintness→ general convulsion T.*
5 (100)	R.	L. arm, moderate	L. arm, moderate	—	(1) Aphasia→ tonic adversive head, eyes to L.→ loss of consciousness
6 (915)	L.	R. arm, R. leg, moderate	R. arm, R. leg, moderate	Aphasia	(1) Pins and needles R. leg→ R. thigh→ clonic R. foot, R. arm→ tonic jaw T.
7 (860)	R.	L. arm, L. leg, moderate	L. hand, moderate	Aphasia	(1) Tonic L. leg, painful cramp→ clonic L. leg. (2) Pain L. face→ clonic L. face→ L. leg→ L. electric shock sensation (not arm). (3) (2) followed by loss of consciousness. No general convulsion T.
8 (512)	L.	R. arm, moderate	R. arm, moderate	Aphasia	(1) R. arm very cold→ R. leg (2) Cry→ general convulsion. (3) R. arm jerks with noise T.
9 (49)	L.	R. leg, R. arm, L. leg, moderate	R. leg, L. leg, R. arm, moderate	R. visual inattention	(1) Paralysed or weak R. arm→ R. leg→ falls to right→ loss of consciousness (brief general convulsion) T.
10 (742)	L.	R. hand, moderate	R. hand, moderate	Slight aphasia	(1) Agnosia R. arm, R. leg for 20 mins.
11 (176)	R.	L. hand, moderate	L. hand, moderate	—	(1) Clonic L. hand→ tonic L. hand, L. fingers. (2) General convulsion in sleep
12 (209)	L.	R. arm, R. leg, moderate	R. arm, R. leg, moderate	—	(1) Clonic R. thumb→ R. fingers (index first)→ tonic R. hand→ paralysed R. hand
13 (816)	R.	L. arm, L. leg, slight	L. arm, L. leg, slight	—	(1) Clonic L. foot→ tonic L. arm→ loss of consciousness. (2) Clonic L. foot, L. arm
14 (935)	L.	R. arm, R. leg, severe	Nil	—	(1) Tonic-clonic R. arm, R. hand. (2) Clonic R. hand→ R. arm→ R. face→ loss of consciousness
15 (776)	R.	L. arm, moderate	L. arm, moderate	—	(1) Clonic L. arm→ L. leg→ loss of consciousness. (2) Numbness L. side→ clonic→ loss of consciousness. (3) L. arm numbness, tonic→ L. side (" horrible feeling ")
GROUP 2.—*Wounds in Rolandic region causing more sensory than motor loss*					
16 (458)	R.	Nil	L. thumb and index	—	(1) Clonic L. thumb→ tonic hand→ clonic L. arm→ loss of consciousness. (2) Numbness L. hand→ tonic L. hand→ clonic L. hand T.
17 (273)	L.	Nil	R. hand, R. face, severe	Aphasia	(1) Clonic R. face→ aphasia→ R. hand weak for ½ hr. (2) Adversive tonic head→ tonic R. arm→ loss of consciousness. (3) Tingling R. foot→ as in (2)
18 (2656)	R.	Nil	L. hand, moderate (ulnar)	—	(1) Stinging L. hand→ L. shoulder→ L. leg→ L. abdomen→ clonic L. face→ choking→ loss of consciousness (L. side convulsed). (2) Electric shock sensation L. neck. (3) Electric shock sensation L. hand, L. foot
19 (815)	L.	Nil	R. hand, moderate (ulnar)	—	(1) Pins and needles R. upper lip→ R. hand→ R. elbow→ R. foot→ R. flank→ vision defective. (2) Visual blackout (? postural) T.
20 (975)	R.	L. arm, L. face, slight	L. hand, L. face, moderate	Lower quadrantanopia	(1) (early only) Electric shock sensation L. hand to L. shoulder→ clonic R. shoulder. (2) Severe pain L. arm→ face→ eye→ loss of consciousness (general convulsion). (2) May be preceded for a day or two by numbness L. arm T.
21 (884)	L.	R. arm, slight	R. hand, severe	Aphasia	(1) Clonic R. hand→ ringing R. ear→ loss of consciousness and general convulsion. (2) Intense change of temperature R. fingers→ R. arm→ R. cheek (R. hand sweats). (3) Agnosia R. face and head T.
22 (775)	R.	Nil	L. hand, moderate (ulnar)	—	(1) Numbness L. hand→ paralysed or weak L. hand
23 (231)	L.	R. hand, slight	R. hand and upper lip moderate	Sensory aphasia	(1) Numbness R. hand→ clonic R. hand→ cold R. face→ R. eyelid and lip (R. leg may twitch). (2) Eyes to R→ cry→ loss of consciousness→ tonic fit
24 (432)	L.	Nil	R. hand, severe (early)	Aphasia	(1) Clonic head→ adversive tonic→ loss of consciousness with general convulsion
25 (8)	R.	Nil	L. arm, L. leg, moderate	—	(1) Clonic L. face. (2) Clonic L. arm→ L. arm paralysis 3–4 min.
26 (44)	R.	L. arm, L. leg, slight	L. arm, L. leg, severe	Slight loss L. visual field	(1) Clonic L. leg→ L. arm
27 (171)	L.	R. arm, R. leg, slight	R. arm, R. leg, severe	R. hemianopia	(1) Tonic R. arm R. face→ clonic R. arm, R. face, aphasia
28 (184)	L.	R. arm, R. leg, slight	R. arm, R. leg, severe	—	(1) Clonic R. leg→ R. arm (numbness after). (2) (1)→ loss of consciousness. (3) (1)→ aphasia
29 (905)	R.	Nil	L. leg, slight	—	(1) Clonic L. leg→ clonic L. abdomen. (2) (1)→ L. arm, L. hand→ tonic adversive head to L.
30 (189)	R.	L. arm, L. leg, slight	L. hemianopia	—	(1) Pins and needles L. face. (2) Pins and needles L. hand→ L. face→ L. leg→ heat L. arm, L. leg. (3) Adversive tonic head to L.→ loss of consciousness→ general convulsion T.
31 (17)	R.	L. arm, L. leg, slight	L. arm, L. leg, moderate	—	(1) Numbness L. leg→ L. arm→ L. chest. (2) (1)→ tonic adversive head to L. (dribble saliva)

*The cases are divided into seven groups according to type and degree of deficit. The second case number refers to the case index. " T " indicates that the case is described in the text.

†When a focal fit proceeds to loss of consciousness, this is always indicated. If a cerebral abscess developed this is mentioned.

AND VISUAL DEFICIT, AND TYPES OF FIT IN 83 CASES*

TRACINGS OF SKULL RADIOGRAPHS‡



‡Site of skull penetration is shaded; metal foreign bodies are dense black. Bone chips in the brain appear as triangles (where pre-operation radiographs are available). An outline of the ventricles as seen by air encephalography is sometimes shown.

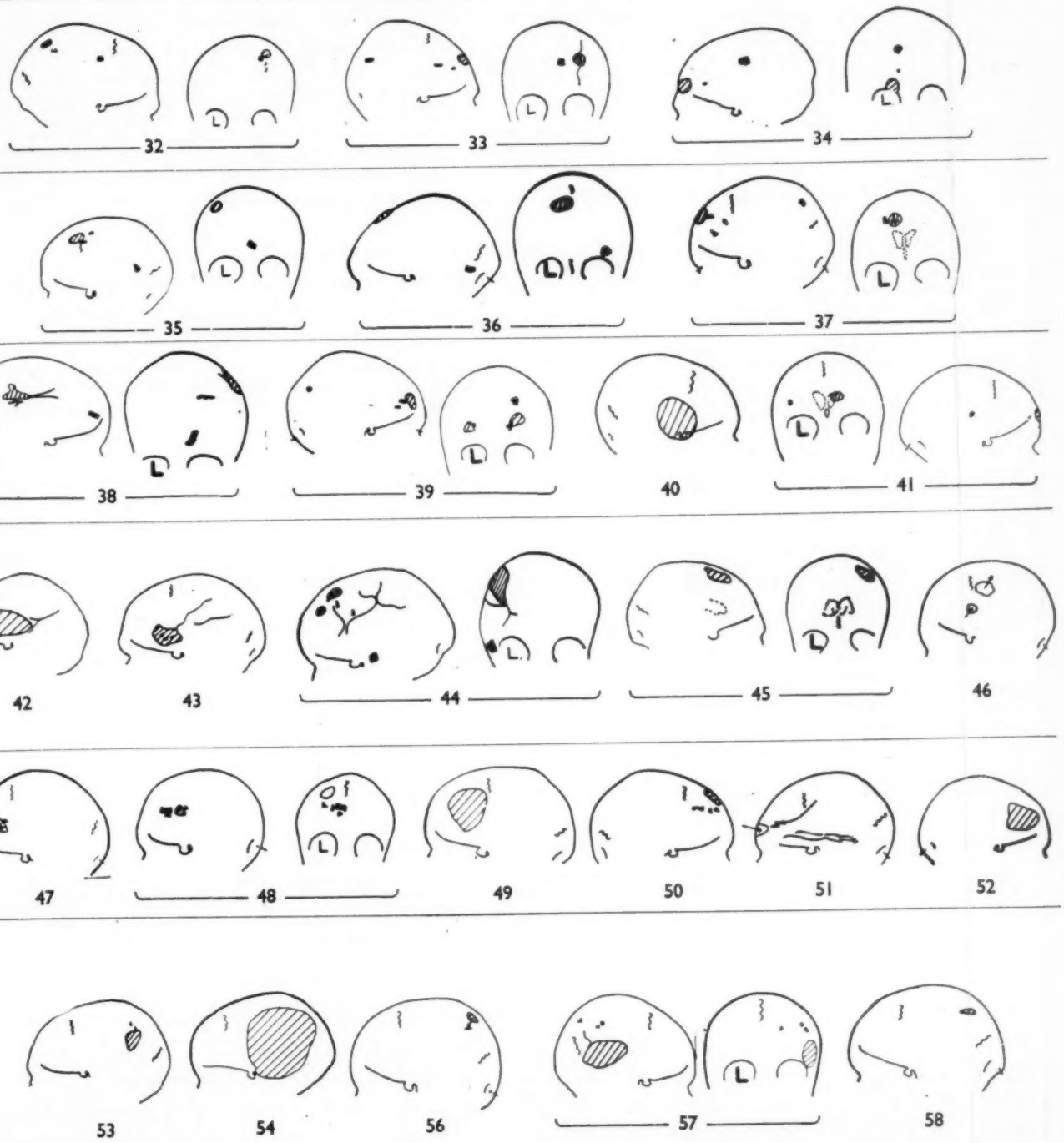
[*Continued overleaf*

TABLE IX—

Case and Index Nos.	Side	Motor Loss	Cortical Sensory Loss	Other	Type of Fit
			GROUP 3.—*Wounds in which a metal fragment travelling in the sagittal plane undercuts the Rolandic area but only causing a limited degree of sensori-motor loss*		
32 (187)	R.	L. arm, L. leg, moderate	L. leg, moderate	—	(1) Tonic eyes→ L. arm. (2) Clonic foot. (3) Dizzy→ fall (no loss of consciousness) T.
33 (782)	R.	L. arm, L. leg, severe (early)	Nil	Aphasia early	Clonic L. foot→ L. leg→ L. shoulder→ sternomastoid→ L. triceps (focal status for 10 days)
34 (168)	L.	R. face, slight	Nil	L. frontal abscess	(1) General convulsion, no aura. (2) Clonic R. hand→ aphasia→ clonic R. face→ general convulsion (clonic on R. only)
35 (891)	L.	R. arm, R. leg, slight	R. arm, R. leg, slight	—	Adversive tonic head to R.→ tonic R. arm, wrist, elbow→ clonic foot→ L.→ loss of consciousness (weak R. arm and R leg for 20 min. after). T.
36 (399)	R.→ L.	R. arm, R. leg, slight	Nil	—	(1) Numbness L. arm→ agnosia L. arm→ paralysed or weak L. arm. (2) As in (1)→ L. leg. (3) Giddiness. T.
37 (2746)	L.	R. arm, slight	Nil	—	(1) Numbness, R. hand→ R. arm→ shoulder→ R. leg and jaw→ loss of consciousness (general convulsion). (2) (early) Clonic R. face→ R. leg, L. leg
38 (463)	R.	L. arm, L. leg, moderate	L. arm, L. leg, moderate	Hemianopia	(1) Tonic L. hand→ clonic→ loss of consciousness (general convulsion) (2) Electric shock sensation L. arm→ L. face→ clonic L. face
39 (2859)	R.	L. arm, L. face, slight	L. arm, L. face, slight	—	(1) Feeling of band L. wrist→ tonic L. hand→ clonic L. fingers→ →face→ loss of consciousness. (2) Tonic jaw→ burning L. hand→ arm→ loss of consciousness. (3) (early) R. "focal motor"
40 (849)	R.	L. hand, slight	L. hand, slight	—	(1) Numbness all L. side (giddy)→ jerk L. arm, L. leg. (2) Pins and needles L. arm→ burning (severe)→ trunk, L. leg→ cold
41 (522)	R. & L.	Nil (early R. arm, R. leg)	Nil	Lower R. quadrantanopia, aphasia	(1) Numbness R. arm→ R. face (paralysed or weak R. arm)→ twitching R. arm→ R. face. (2) Light R. visual field→ R. triceps feels torn. (3) Sudden giddiness→ staggers
			GROUP 4.—*Frontal or temporal wounds with little or no sensori-motor loss*		
42 (733)	L.	R. hand, slight	—	Lower quadrantanopia, aphasia	(1) Aphasia→ hot R. hand and shoulder→ clonic R. hand, R. arm→ general convulsion. (2) Aphasia→ loss of consciousness (general convulsion) T.
43 (704)	L.	R. arm, R. leg	R. arm (slight)	—	(1) Clonic with pins and needles R. fingers→ hand→ arm. (2) (1)→ clonic R. face, R. leg→ aphasia. (3) General convulsion (no aura)
44 (864)	L.	R. arm, slight	R. arm, slight	Aphasia	(1) Hot R. hand→ R. arm. (2) (1) plus clonic R. hand. (3) Clonic 4th and 5th fingers→ R. hand, arm→ general convulsion T.
45 (723)	R.	—	—	—	(1) Pins and needles R. fingers→ numbness R. hand→ clonic R. fingers→ tonic R. arm. (2) as (1)→ loss of consciousness
46 (948)	L.	—	—	Slight aphasia	(1) Tonic adversive head to R.→ tonic R. arm→ tonic L. arm→ clonic R. arm L. arm
47 (371)	L.	—	—	—	Clonic eyes→ general convulsion (clonic R. face, arm, leg)
48 (207)	L.	—	—	—	Tonic eyes→ fall (spiral movement), no general convulsion
49 (813)	R.	—	—	—	Adversive tonic head to L.→ loss of consciousness (clonic L. arm, L. leg)
50 (593)	R.	—	—	—	(1) General convulsion in sleep. (2) Clonic L. face, L. arm→ loss of consciousness (general convulsion)
51 (814)	L.	R. face, slight	—	—	(1) Numbness R. face→ R. arm→ paralysed or weak R. hand. (2) (1)→ loss of consciousness. (3) (2)→ general convulsion
52 (36)	R.	R. face, slight	—	—	(1) General convulsion, no aura. (2) Clonic R. arm, R. face, eyes adversive clonic to R. (between 2 general convulsive attacks) T.
			GROUP 5.—*Posterior parietal wounds with little or no sensori-motor loss*		
53 (510)	L.	—	R. hand, slight	Lower quadrantanopia	(1) Visual spot→ phantom R. arm movements. (2) R. arm numb→ clonic R. arm. (3) general convulsion T.
54 (922)	L.	—	—	Lower quadrantanopia, aphasia	(1) Hot R. hand→ arm→ edge of face→ tonic hand→ clonic R. arm T.
55 (467)	R.	—	—	Radiograph, normal	(1) Paralysed or weak R. leg, L. leg→ fall→ loss of consciousness (momentary). (2) Epigastric sensation→ burning L. hand→ arm→ shoulder
56 (390)	L.	—	—	R. attention hemianopia, aphasia	(1) General convulsion (no aura). (2) Paralysed or weak R. hand
57 (571)	R.	L. arm, L. leg (early)	L. arm, L. leg (early)	L. hemianopia. Abscess	(1) (early only) Adversive tonic head, eyes to L.→ tonic L. arm→general convulsion. (2) Paralysed or weak L. hand→ loss of consciousness (general convulsion)
58 (71)	L.	—	R. arm, slight	Lower quadrantanopia	(1) Pale→ loss of consciousness (general convulsion). (2) Phantom R. arm above head (clenched) T.

continued

TRACINGS OF SKULL RADIOGRAPHS‡



[*Continued overleaf*

TABLE IX—

Case and Index Nos.	Side	Motor Loss	Cortical Sensory Loss	Other	Type of Fit
59 (266)	R.	R. arm, L. leg, slight	L. arm, L. leg, slight	Hemianopia	(1) Agnosia L. hand. (2) Agnosia L. hand → visual → general convulsion
60 (931)	L.	—	—	Lower quadrantanopia	(1) R. hemianopia, clonic eyelids → loss of consciousness. (2) Clonic R. arm → clonic R. leg
61 (485)	R.	—	—	L. hemianopia	(1) Pins and needles L. side. (2) (1) → clonic L. hand, L. leg → hemianopia. (3) as (2) → loss of consciousness (general convulsion)
62 (800)	L.	—	—	Dyslexia	(1) Funny feeling R. face → loss of consciousness (general convulsion). (2) Tinnitus → loss of consciousness (general convulsion)
63 (896)	L. → R.	—	—	Aphasia bilateral, visual field defect	(1) Clonic L. face → L. hand. (2) Clonic L. leg → L. hand → L. face. (3) As in (1) then → loss of consciousness. (4) General convulsive status with focal clonic L. hand, L. face intermittent between general convulsion attacks. (5) Aphasia → general paralysis or weakness T.
					GROUP 6.—*Cases with severe hemiplegia, sensory and motor, but no hemianopia*
64 (470)	Midline	R. leg, L. leg, R. arm, severe	R. leg, L. leg, severe	—	(1) Adversive tonic head to R. → R. shoulder tonic → R. shoulder clonic
65 (708)	L.	R. arm, R. leg, severe	R. arm, R. leg, severe	Aphasia	(1) General tonic → loss of consciousness. (2) Tonic R. arm T.
66 (53)	L.	R. arm, R. leg, moderate	R. arm, R. leg, moderate	Aphasia	(1) Tonic-clonic R. hand → R. foot. (2) Cry → general convulsion, clonic R. side only
67 (419)	R.	L. arm, L. leg, severe	L. arm, L. leg, severe	Aphasia	(1) Tonic adversive head to L. → loss of consciousness → clonic L. face, arm, leg → R. leg, arm, face. (2) Epigastric → vertigo → clonic L. hand → L. leg
68 (853)	R.	L. arm, L. leg, severe	L. arm, L. leg, moderate	—	(1) Tonic adversive head to L. (2) Clonic L. foot focal status (early only) T.
69 (702)	L.	R. arm, R. leg, moderate	R. arm, R. leg, severe	—	(1) Vertigo to L. → aphasia to hemianopia → tonic R. hand (stopped by gripping hand). (2) Adversive tonic head to R. → loss of consciousness. (3) General convulsion → no aura
70 (2697)	R.	R. arm, R. leg, severe	R. arm, R. leg, severe	—	(1) L. fingers clonic → L. arm. (2) As (1) → adversive tonic head to L. → loss of consciousness (general convulsion)
71 (54)	L.	R. arm, R. leg, severe	R. arm, R. leg, severe	—	(1) Tonic-clonic R. shoulder → R. leg. (2) As (1) → loss of consciousness. (3) General convulsion, no aura (early)
72 (928)	R.	L. arm, L. leg, severe	L. arm, L. leg, severe	—	(1) Fall → loss of consciousness. (2) Twitching L. leg → loss of consciousness
73 (959)	L. → R.	L. arm, L. leg, severe	L. arm, L. leg, moderate	—	(1) (Early) painful spasms L. leg. (2) Vibration R. arm → R. leg
74 (706)	L.	R. arm, R. leg, severe	R. arm, R. leg, severe	Aphasia	(1) Tonic R. face → R. arm. (2) Clonic R. face → R. arm → R. leg. (3) Clonic R. abdomen, thorax → pain R. abdomen, R. thorax, R. neck T.
75 (821)	R. → L.	L. arm, L. leg, severe	L. arm, L. leg, severe	—	(1) Clonic L. arm → numbness L. arm → loss of consciousness → general convulsion. (2) Sudden jerk T.
					GROUP 7.—*Cases with hemiplegia and hemianopia*
76 (534)	R.	L. arm, L. leg, moderate	L. arm, L. leg, moderate	Hemianopia, spatial loss	(1) Phantom movements L. fingers. (2) As (1) → tonic L. hand → clonic L. arm. (3) As (2) → visual hallucination (formed) → loss of consciousness T.
77 (937)	R.	L. arm, L. leg, severe	L. arm, L. leg, moderate	Hemianopia	(1) Electric shock sensation L. arm → clonic L. arm → face → leg (L. arm, L. leg paralysed or weak 20 min.). (2) Tonic L. arm → loss of consciousness (gereral convulsion) T.
78 (157)	R.	L. arm, L. leg, severe	L. arm, L. leg, severe	Hemianopia	(1) Tonic-clonic L. face, tonic adversive head to L. → L. arm, L. leg. (2) As (1) → loss of consciousness
79 (762)	R.	L. arm, L. leg, severe	L. arm, L. leg, severe	Hemianopia, athetosis	(1) Early focal status L. hand T.
80 (173)	R.	L. arm, L. leg, moderate	L. arm, L. leg, severe	Lower quadrantanopia	(1) Clonic L. side. (2) General convulsion, no aura
81 (518)	R.	L. arm, L. leg, moderate	L. arm, L. leg, severe	Lower quadrantanopia	(1) Clonic L. shoulder → L. leg → loss of consciousness (general convulsion)
82 (861)	L.	R. arm, R. leg, severe	R. arm, R. leg, severe	Hemianopia	(1) Clonic R. hand (15 min.) → loss of consciousness. (2) Clonic R. hand → clonic R. leg
83 (917)	R.	R. arm, L. face, severe	R. arm, R. leg, severe	Lower quadrantanopia	(1) Agnosia L. arm, L. leg, L. face → adversive tonic head to L. → loss of consciousness (clonic L. arm, L. leg). (2) Loss of vision → dizzy

ontinued

TRACINGS OF SKULL RADIOGRAPHS‡

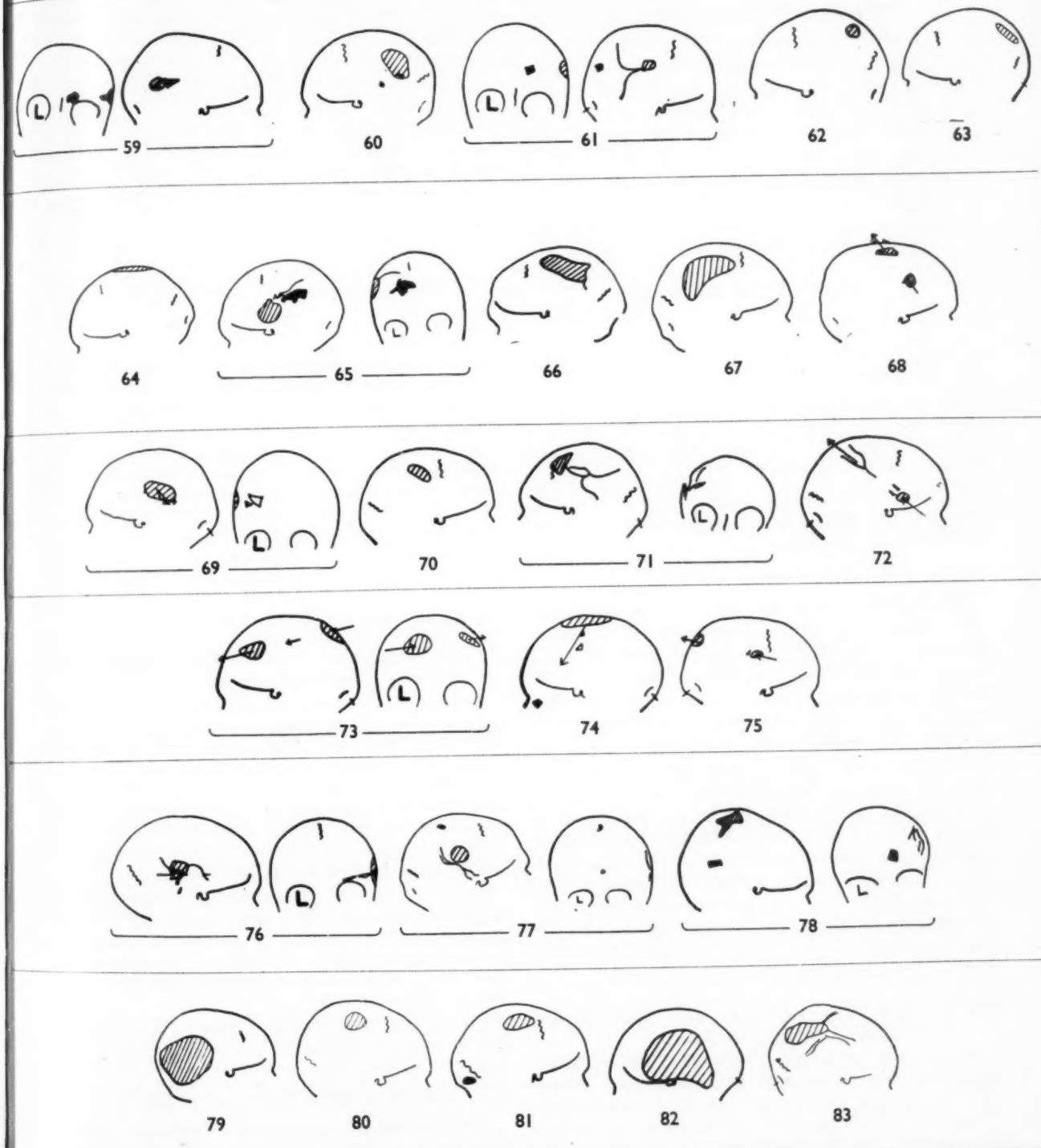


TABLE X

PRESENTING FOCAL AURAS COMPARED TO SENSORI-MOTOR DEFICIT USING SEVEN GROUPS IN TABLE IX

Groups from Table IX		Small Wounds					Hemiplegia	Hemiplegia and Hemianopia	
		M = S M > S	S > M	Undercutting	Fronto-temporal	Posterior Parietal			
		1	2	3	4	5	6	7	
	Totals	20	25	14	13	1	14	8	106
Motor	Adversive	—	3	1	3	1	4	—	12
	Tonic	5	1	3	—	—	4	2	15
	Clonic	6	8	4	5	2	4	3	32
	Jerk	1	—	—	—	—	2	—	3
	Inhibitory	1	—	—	1	3	—	—	5
Sensory	Tingling, pins and needles	3	4	1	1	2	—	—	11
	Numbness	1	4	4	1	1	—	—	11
	Pain	1	1	—	—	—	—	—	2
	Hot and cold	1	1	—	2	1	—	—	5
	Electric shock	—	2	1	—	—	—	1	4
	Agnosia	1	1	—	—	1	—	1	4
	Phantom	—	—	—	—	1	—	1	2

S = sensory deficit. M = motor deficit.

appreciated. Aphasia was more marked on the motor than the sensory side.

Fits.—**1.** Intermittent slow tonic contraction of the triceps muscle in the right arm occurred. This caused a slow extension of the arm which subsequently relaxed to the position of semi-flexion.

2. There was a sudden generalized tonic stiffening, then loss of consciousness and generalized clonic movements.

Focal Sensory Attacks

The various types of sensory discharge also show some differences in their capacity for detailed reference (Table VIII). For example, the sensation of pins and needles may be referred precisely, as in the following cases (Nos. 6, 19). Sensory auras seem to differ, however, from the clonic motor auras in the rapidity with which they spread, for though they may begin in some localized part of a limb, it is usual for them to spread quickly to involve at least the whole limb. The occurrence of a sensory aura which remains localized for hours or even days, as in focal motor status, has never been recorded in these cases. Another difference is seen in the fact that a motor fit will readily develop after destruction of the motor cortex, but as will be considered later, sensory fits are only described when a part at least of the sensory cortex is intact.

CASE 6. **Focal Sensory Attacks with Rapid Spread Leading to Focal Motor Attacks**

A left fronto-parietal wound soon after wounding caused right hemiparesis with global dysphasia. There was sensory loss in the right hand, stereognosis and movement sense being markedly reduced: the leg was less affected. The permanent disability included spastic hemiparesis with reduction of joint sense in fingers and toes. There was some hyperpathia in the left hand, and some residual dysphasia, especially at times of emotion.

Fits.—**1.** A pins-and-needles feeling suddenly appeared in the right shin. This passed rapidly up the leg to the thigh, and was followed by a jerking of the foot and then of the arm. The jaw was then tightly clenched, but there was no clonic movement. There was no loss of consciousness.

These attacks could sometimes be stopped by using the muscles of the affected limb as strongly as possible. This applied both to the leg and arm.

CASE 19. **Focal Sensory Attacks with Extensive Spread and Focal Visual Epilepsy**

In a left anterior parietal wound soon after wounding there was a right hemiparesis and aphasia and some continuous, ill-defined, spontaneous pain in the right upper limb. Passive movement sense was reduced in this limb, but pin-prick was appreciated. Some years later there was slight right hemiparesis, with reduction of passive movement sense and two-point touch in the right hand, mainly on the ulnar border. No weakness was present, and there was no dysphasia.

Fits.—**1.** A sudden pins-and-needles feeling appeared in the right upper lip. This then passed to the hand and up the arm to the elbow. Then it started in the right foot and the right flank. At this time the patient found difficulty in concentrating, and complained of not being able to see properly.

2. A sudden visual blackout lasted for a few seconds only. There was no loss of consciousness.

Focal Attacks in the Lower Limb

One striking feature of Table VIII is the relative infrequency of attacks beginning in the lower limbs.

Of the total 135 types of attack analysed, only 17 started in the lower compared with 69 in the upper limb. The disparity occurred in both motor and sensory attacks. This does not represent simply a lower percentage of wounds involving the leg area, as may be seen from Fig. 2 (Part 1), when the distribution of all wounds with or without epilepsy was considered. Indeed, detailed consideration of the only four cases which showed clonic motor attacks starting in the foot suggests that special physiological conditions may be required for ictal firing of this area. In one the attacks only occurred just before going to sleep, while in two others they only occurred during the first few weeks after wounding.

CASE 32. **Focal Motor Attacks Starting in the Foot and Adversive Attacks**

A right posterior parietal to frontal wound undercutting cortex early after wounding caused left hemiplegia and homonymous hemianopia. There was loss of all forms of sensation in the left leg below the knee, and to a lesser degree in the left hand. Some years later spastic left hemiparesis persisted, the leg being more affected than the arm. There was cortical sensory impairment in the left leg and also slight change in the appreciation of pin-prick. No marked sensory change in the arm was noted.

Fits.—**1.** There was occasional clonic jerking of the left foot only with no tonic stiffening. This only occurred just before going to sleep.

2. The eyes suddenly turned to the left, then the left arm jerked and was drawn up to the face. There was no loss of consciousness, and the leg was not involved.

3. A sudden dizzy feeling occurred with falling but no loss of consciousness.

CASE 13. **Clonic Focal Fits of Foot and Occasional Loss of Consciousness**

There was a right anterior parietal brain wound, and, some years after wounding, slight spastic weakness of the left arm and leg with some sensory loss of cortical type, persisted.

Fits.—**1.** Clonic movement of the left foot occurred at the same time as clonic jerking of the left hand and arm. The fit then ceased.

2. There were sudden clonic movements of the left foot, the left arm was then drawn up in a tonic movement and consciousness was lost.

Cases 33 and 68, of partial continuous epilepsy of the foot, also illustrate this point, and are considered later. The foregoing case records illustrate certain general features which may be seen at the *onset* of any focal motor or sensory attack. However, the subsequent course of the attack which is next considered, and the detailed content of various types of sensori-motor fit, especially some of the more unusual ones mentioned later, also provide material of interest in the study of cerebral function.

SPREAD OF INITIAL ATTACK

Great efforts have been made in this study to collect reliable information as to the spread of the epileptic aura, and to analyse the results in relation to possible directions, rates, or patterns of spread of the different varieties described. Several features of this analysis have been recognized and described, but we are fully conscious of the likelihood that the facts collected supply additional information of importance which we have so far failed to recognize and extract from the recorded observations.

Extent and Rate of Spread

Definite information about the rate of spread is scanty. It is usually a matter of seconds, for instance, for the common sensory aura of pins and needles starting in the hand to reach the shoulder or the edge of the face. In the case of focal clonic fits, however, the rate of spread is often much slower, and in the following case, where accurate timing was done, lasted for about eight minutes.

CASE 585 (not included in tables). **Focal Clonic Motor and Focal Sensory Attacks**

A right frontal brain wound (Fig. 3), with indriven bone fragments which had reached the head of the caudate nucleus, caused left spastic hemiplegia with athetotic posture of the limbs, exaggerated by any attempts at voluntary movement. In the foot this produced a spastic extension of the great toe so uncomfortable as to require amputation. Fits started some months after wounding as follows. There were sudden clonic movements of the face, which passed down to the shoulder, then to the elbow (but not the hand), to the thoracic muscles, to the thigh, and to the foot. The attacks then ceased. Eight minutes elapsed between the onset of facial movements and those in the foot. Sometimes after a motor attack there was a sudden tingling sensation in the left fingers which passed rapidly up the arm to the shoulder, to the edge of the face, then down the left flank and from the thigh down to the toes.

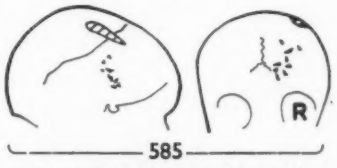


FIG. 3.—Skull tracing of Case 585.

It has already been pointed out that sensory auras spread quickly, also that sensations of pins and needles or tingling may have a very local and precise reference. Other types of sensory aura such as pain, heat or cold, often affect a larger area

from the start, but they too show the tendency to rapid spread. These features are shown in the following cases :—

CASE 8. **Focal Thermal Sensory Attacks of Wide Reference and Grand Mal attacks and Myoclonic Jerks**

A left parietal brain wound shortly after wounding caused right hemiparesis with sensory loss in the right limbs, and global dysphasia, but no field defect. Some years later there was spastic weakness of the upper limb with cortical sensory loss and some loss of pain sense in the finger tips only.

Fits.—**1.** The right arm suddenly felt intensely cold. This spread rapidly to the leg, and the attack ceased.

2. The right arm would suddenly give an uncontrollable jerk. This commonly followed some stimulus such as an unexpected noise.

3. There was a sudden cry, then loss of consciousness and a generalized convulsion.

CASE 54. **Focal Sensory Attacks of Heat with Extensive Spread followed by Motor Involvement**

A left posterior parietal brain wound soon after wounding caused gross global dysphasia with right homonymous hemianopia and some weakness of the right hand. Some years later dysphasia was present, though dysgraphia and dyslexia were more marked. There was a lower right homonymous field defect, but no weakness or sensory loss.

Fits.—A sudden hot feeling occurred in the right hand. This was not painful, but like holding it near a fire. It passed rapidly up the hand and arm to the edge of the face, and then the hand was drawn into a tonic spasm and there was some clonic jerking at the elbow.

Inhibitory auras, whether sensory or motor, seem always to affect a large area *ab initio*. The whole of a limb is involved, and this usually spreads to the whole of one side of the body. Indeed, inhibitory auras tend to be more widespread also in the sense that they often involve both sensory and motor functions.

CASE 36. **Inhibitory Sensory Attacks of Wide Reference and Some Motor Inhibition**

A right frontal to left occipital brain wound early after wounding caused slight weakness of the left arm and leg, but no detectable sensory change. Some years later there were no abnormal signs in the nervous system.

Fits.—**1.** A sudden numbness occurred in the left arm. This was a negative feeling as if the arm were not fully there. While this lasted the arm could not be used properly.

2. As above, but the sensation passed rapidly after onset in the left arm to the left leg. The same motor disability was also noted here.

CASE 9. **Motor Inhibitory Attacks with Wide Reference as Aura to Generalized Tonic Fit**

A left mid-parietal parasagittal wound shortly after wounding caused spastic paralysis of both legs, with flaccid weakness of the right arm, and severe loss to all forms of sensation including pain and light touch in those limbs. There was an attention defect in the right visual field. Some years later there was still weakness of the right arm and both legs, with some increase in tone. Passive movement sense and two-point touch were lost in the toes, and impaired in the right hand.

Fits.—The right arm suddenly became powerless and fell to the side. This rapidly spread to the right leg, so that the patient fell to the right side. Shortly thereafter consciousness was lost, and a brief general tonic stiffening occurred.

Direction of Cortical Spread

When a number of cases are available for study the order in which focal phenomena may follow each other is clearly of significance in relation to the study of cerebral physiology, especially if, as appears from this series, the spread tends to be in certain specific directions. Table XI analyses this spread of the focal phenomena one to another. For this table a group of cases with sensory or motor fits is analysed as regards all the focal phenomena which could be described in detail. (It is the change from one type of aura to another which is recorded so that more than one entry often appears for one case.) It must also be emphasized that the *cessation* of an epileptic phenomenon is just as positive an event (inhibition) as is the spread to another form of discharge, so that special attention is devoted to those forms of aura which precede a complete arrest of the fit. Also the spread to cause loss of consciousness and a general convulsion is of special physiological interest, and those auras proceeding to loss of consciousness are indicated.

Some remarkable facts emerge from Table XI. In the first place it becomes apparent that a sensory aura frequently passed to a motor aura, whereas spread from motor to sensory is rarely recorded. In no case did tingling or pins and needles follow a motor aura, and in only one case is there a clear record of clonic focal movements on one side being succeeded by the common somatic sensory aura of numbness. In the other few instances of sensory phenomena following motor, they either involved the special senses, auditory or visual, or a sensation such as heat or pain, which are uncommon types of aura.

Case 76 illustrates in some of the fits the spread of clonic movement to a visual aura, and the following three cases also illustrate some of these unusual types of spread.

TABLE XI

SEQUENCE OF EVENTS FOLLOWING MANY FOCAL AURAS*

			Subsequent Event																
			Totals	Tingling, pins and needles	Pain	Shock	Heat and cold	Numbness	Agnosia	Phantom	Adversive	Tonic	Clonic	Jerk	Paralysis	Aphasia	Loss of consciousness	Fit ceased	Other
Focal Auras	Sensory	Tingling, pins and needles	24	**9**	—	—	2	—	—	—	1	—	5	—	—	1	1	4	1
		Pain	6	—	—	—	—	—	—	—	—	—	1	—	—	—	1	3	1
		Electric shock	4	—	—	**1**	—	—	—	—	—	—	2	—	—	—	—	1	—
		Heat or cold	16	—	—	—	**6**	—	—	—	—	1	2	1	—	—	1	5	—
		Numbness	19	—	—	—	—	**5**	1	—	1	1	4	2	3	—	1	1	—
		Agnosia	7	—	—	—	—	—	**1**	—	1	—	—	—	1	—	—	3	1
		Phantom	4	—	—	—	—	—	—	—	—	1	—	—	—	—	—	3	—
	Motor	Adversive	17	—	—	—	—	—	—	—	—	**6**	—	—	—	—	8	3	—
		Tonic	38	—	—	—	1	—	—	—	—	**3**	16	—	1	—	7	10	—
		Clonic	94	—	1	—	2	1	—	—	3	6	**23**	—	3	3	20	30	2
		Jerk	6	—	—	—	—	—	—	—	—	—	1	—	—	—	1	4	—
		Paralysis	12	—	—	—	—	—	—	—	—	—	—	—	**1**	—	4	7	—
		Aphasia	7	—	—	—	1	—	—	—	1	—	1	—	1	—	1	1	1
		Other	13	—	1	—	1	—	—	1	—	1	2	—	—	1	4	2	—
		Totals	267	9	2	1	13	6	2	1	7	19	57	3	10	5	49	77	6

* The "subsequent" events may be a spread of the same type of aura to another region (squared bold numbers), or spread to another type of aura, or to loss of consciousness, or to cessation of the fit.

CASE 75. **Clonic Motor Attack followed by Sensory Aura followed by Grand Mal**

A right frontal to parietal wound (through and through) early after wounding caused spastic left hemiplegia, with gross sensory loss. Some years later there was still severe hemiparesis more in the arm than in the leg, and cortical sensory loss of the same distribution.

Fits.—Sudden clonic movements occurred in the right hand and leg, a numb dead feeling followed in the hand and leg, then consciousness was lost and clonic movements ceased, while generalized tonic stiffening occurred, which was then followed by generalized clonic movements.

CASE 21. **Focal Clonic Attacks Passing to an Auditory Sensation before Grand Mal and Focal Thermal Focal Agnosia Attacks**

A left parietal wound soon after wounding produced severe global dysphasia. There was also weakness of the right arm and leg and marked cortical sensory loss in the right hand and face. Some years later there was a residual dysphasia of expressive and receptive types. There was loss of position sense and stereognosis in the right hand together with some change in the appreciation of pain. There was a very slight spastic weakness of the arm, but the leg appeared normal.

Fits.—**1.** There was a sudden twitching of the right hand, then a ringing noise in the right ear, then loss of consciousness. This was followed by generalized stiffening, but no generalized clonic element.

2. Sudden intense feeling in the finger-tips ran rapidly up the right arm to the cheek. The feeling was of change of temperature, but was so intense that it seemed sometimes freezing and sometimes burning. The hand sweated profusely during this attack.

3. A sudden feeling as if the face and head on the right had ceased to exist.

CASE 74. **Focal Clonic Aura followed by Focal Pain and Other Types of Motor Attack**

A left high parietal to inferior frontal wound caused early right hemiplegia and hemianaesthesia. Later a marked spastic paresis in the right hand with cortical sensory loss persisted. The right leg was a little weak and spastic with some passive movement sense loss. There was gross dysphasia and some dementia.

Fits.—**1.** Twitching of the right abdomen proceeded to the right intercostal muscles and then severe gripping pain occurred in the abdomen and chest wall and passed up to the neck.

2. There was sudden stiffness and numbness of the right face but no movements.

3. Clonic twitching occurred in the right face, then in the right abdomen and in the right leg.

4. (early) A right-sided clonic fit occurred in the arm and then in the leg.

It might be argued that the occurrence of involuntary movement is so striking for the patient as to allow subsequent numbness in the part affected to pass unremarked, whereas pain or a special sense aura, being more obtrusive, would be noted. However, this is unlikely to account entirely for the great difference in frequency of these two types of spread: apart from the case quoted above (No. 75) there were two others in which numbness developed and spread *pari passu* with a clonic or tonic movement (Cases 3 and 43). It seems clear that while the spread of a somatic sensory aura to a motor one is quite usual, the reverse method of spread is quite exceptional.

While all forms of sensory aura often spread quickly to a motor aura, there is little tendency for one type of sensory aura to spread to another type. This suggests that the cortical cells concerned with these various sensory functions have easier anatomical access to the motor cortex than to post-central cells concerned with other types of sensation. The only type of sensory aura in this series which proceeded to a general convulsion without report of a motor phase of the aura were Cases 20 and 39, in which the aura was of intense local pain or heat; Case 39 was remarkable in the spread from focal tonic to focal burning, and then loss of consciousness with convulsions involving only the one (the affected) side.

CASE 20. **Aura of Focal Pain Immediately Followed by Grand Mal and Attacks of "Electric Shock" with Clonic Movement**

A right parietal brain wound soon after wounding produced a left hemiparesis with sensory loss in the left hand, and a left homonymous visual field defect. Some years later there was a left inferior quadrantic field defect, a slight spastic weakness of the left hand and face, with sensory loss in the hand and the face of discriminative cortical type.

Fits.—**1.** There was a sudden, intensely unpleasant pain in the whole left arm, which passed up to the face and the corner of the left eye, then consciousness was lost and a general convulsion ensued. The pain in the arm was hard to describe, but phrases used were "unnatural", "intensely unpleasant", "a torture of pain".

2. Sometimes the pattern was as in (1) but preceded by a dead feeling in the arm for a day or so, and was considered as the herald of an attack.

3. The third manifestation was seen only in early fits. Sudden, shock-like feelings occurred in the left hand, which spread rapidly up to the shoulder, and were followed by twitching of the shoulder only.

CASE 39. **Motor Tonic Aura Spreading to Burning Sensation and Other Types of Attack**

A right frontal to posterior parietal brain wound soon after wounding caused left hemiparesis with sensory loss. Some years later there was a slight spasticity and weakness of the left hand and face, some reduction of stereognosis and passive movement sense in the hand, and some two-point discrimination loss in the face.

Fits.—**1.** Tonic clenching of the jaw was followed by intense burning of the left hand. This marched up the arm to the shoulder, consciousness was lost, and a generalized tonic stiffening occurred with clonic movements of the left side only.

2. There was a sudden feeling of constriction as if a tight band was around the left wrist. There was then some tonic stiffening of the hand followed by clonic movements which proceeded up the arm to the face. Consciousness was then lost and convulsions occurred as in (1).

3. Right-sided convulsions occurred with no involvement of the left side; this pattern was only seen in early fits.

The relationship between a clonic and tonic aura is also of interest (Table XI). Sixteen out of 39 tonic episodes became clonic, but only six of the 95 clonic auras changed to tonic. Such "paths of election" for spread are further emphasized in Table XIII so far as the clonic motor auras are concerned. Here it may be seen that in seven out of 18 instances clonic movement in the face passed to loss of consciousness, while loss of consciousness followed directly in only one case of 27 where clonic movement occurred in the thumb or fingers. This is a reflection of the fact that movements starting in the digits tend to show a Jacksonian march if they spread, as can also be seen in this table. It would appear that the areas for face and head representation have very ready access to these mechanisms concerned with loss of consciousness, an observation already implicit in much earlier clinical literature on epilepsy where the common occurrence of loss of consciousness as the aura reached the head was noted.

Table XII extracts some of the information in Table XI from the point of view of comparing the behaviour of motor and sensory auras. Here again there is evidence that the epileptic process moves more easily in one direction than another.

These findings indicate certain physiological patterns for the spread of the epileptic process which deserve further study.

TABLE XII

COMPARISON OF SPREAD OF MOTOR AND SENSORY AURAS

	80 Examples of Sensory Aura	174 Examples of Motor Aura
Spread to sensory..	Same* : 22 (27%) Other : 3 (4%)	6 (3%)
Spread to motor ..	28 (35%)	Same* : 27 (15%) Other : 42 (24%)
Fit ceased	20 (25%)	55 (31%)
Spread to loss of consciousness ..	4 (5%)	41 (24%)
Other	3 (4%)	3 (2%)

* "Same" indicates spread of the same type of aura to another part of the body (see Table XI).

Types of Spontaneous Cessation of Focal Attacks: Post-epileptic Paralysis

The ending of a focal attack is also of interest, and is recorded as occurring after all varieties of aura (Table XI). Clonic motor attacks usually die out gradually with a gradually lengthening interval between each clonic movement. Sometimes they are followed by weakness, though not complete paralysis, of the affected limbs which may last 20–30 minutes, long after all movements have ceased (Todd's paralysis, 1861). There seems nothing in the intensity of the clinical attack to suggest an "exhaustion paralysis" and it seems more likely to be due to involvement or release of some inhibitory mechanism. The following case illustrates this point.

CASE 77. **Focal "Electric Shock" with Clonic and Inhibitory Fits followed by Local Paralysis; Possible Spread to Grand Mal**

A right parietal brain wound was sustained. Some years after wounding there was a left homonymous hemianopia and left spastic hemiparesis, more in the arm than in the leg. No gross sensory change was noted early, but later some loss of stereognosis and two-point touch in the left hand was found.

Fits.—**1.** There was a sudden feeling as of an electric shock in the left elbow, then twitching of the muscles of the left forearm, followed immediately by twitching of the left face and of the left leg below the knee, in that order. At the same time loss of power in the arm and weakness and incoordination on attempted movement of the left leg occurred. This motor effect lasted about 20 minutes.

2. Attacks started as above, but the left arm was raised at the shoulder and the elbow forced backwards. This was followed by loss of consciousness with left-sided generalized clonic movements.

Sensory attacks, on the other hand, when they do not pass over to motor, as they often do, usually end abruptly. At one moment the sensation is still there, and the next moment it has cleared entirely. There seems to be no gradual fading away. This is well shown in the following case where the aura was an inhibitory one of sensory agnosia.

CASE 10. **Focal Inhibitory Sensory Attacks with Agnosia and with Abrupt Ending**

A deep left parietal wound soon after wounding caused right hemiplegia with sensory loss to all modalities, more in the arm than in the leg. There was also dysphasia, more expressive than receptive. Some years later the right hand was weak with increased tone, and there was loss of stereognosis, two-point touch, and passive movement sense. There was also a slight motor dysphasia which emerged when the patient was emotionally upset.

Fits.—The left arm and almost immediately afterwards, the left leg, suddenly seemed to disappear. "There is a feeling that they don't belong to me, and I

TABLE XIII

PATTERN OF SPREAD OF CLONIC FITS*

		Focal Movement or Other Subsequent Event												
		Face	Head and Eyes	Thumb	Hand and Fingers	Arm	Shoulder	Abdomen Trunk	Leg	Foot	Loss of Consciousness	Fit Ceased	Other	Totals
Focal Aura	Face	X	1	—	1	2	—	—	1	—	7	5	1	18
	Head and eyes ..	—	X	—	—	—	—	—	—	—	2	—	1	3
	Thumb	—	—	X	1	—	—	—	—	—	—	—	2	3
	Hand and fingers ..	5	—	—	X	5	—	—	2	2	1	7	2	24
	Arm	4	—	—	1	X	—	—	5	—	5	6	6	27
	Shoulder	—	—	—	—	1	X	—	2	—	1	2	—	6
	Abdomen or trunk ..	—	—	—	—	1	—	X	—	—	—	1	1	3
	Leg	—	—	—	1	2	2	1	1†	—	4	8	1	20
	Foot	—	—	—	—	2	—	—	4	X	—	4	—	10
		9	1	—	4	13	2	1	15	2	20	33	14	114

* Each clonic feature is entered according to list at left of Table. There may, therefore, be several entries for one case, and indeed for one fit.

† Spread from one leg to the other.

look at them with surprise". This attack lasts about 20 minutes, and ends abruptly. There is no loss of consciousness and no further ictal phenomena.

"Jacksonian" Spread

In addition to the transcortical spread from one variety of aura to another, there is the better known type of spread from one part of the body to another. This "Jacksonian march" occurs most classically in some cases of focal clonic attack. In many cases of this group the aura, in fact, begins with a sensory focus and proceeds to clonic motor convulsion. A typical sensory march may also be seen, but, as has been mentioned, this tends to spread more quickly than do the clonic motor attacks.

The following cases illustrate these points, which are also shown in Cases 33, 16, and 6 detailed above.

CASE 66. **Spreading Focal Tonic and Clonic Fits, Grand Mal Attacks, without Aura**

A left parietal brain wound early after wounding caused dysphasia, with right spastic hemiplegia, including the face, and partial right hemianaesthesia to all types of sensation. Some years later there was slight residual dysphasia, most marked in emotional situations, with slight spastic weakness of the arm more than of the leg. Two-point touch appreciation was reduced in the right hand and stereognosis was markedly affected. Passive movement sense was grossly reduced in the right hand and arm up to the elbow. Pin-prick was felt as cold and painful, but was not localized. The leg showed very slight spasticity with sensory changes similar to those in the arm but less marked, and confined mainly to the foot.

Fits.—**1.** The right arm suddenly jerked up to the face, the hand was flexed, and clonic jerks appeared at the wrist for a few seconds. The thumb and fingers were flexed in tonic spasm but did not jerk. Just after the arm started moving, the foot also jerked, but without tonic spasm. There were no facial movements. The movements of the hand could be controlled usually by forcibly extending the right arm with the left. Standing up and taking the weight on the right leg will similarly abolish the movements in that limb.

2. A sudden cry occurred with loss of consciousness, falling, and generalized tonic stiffening. This was followed by jerking of the right side only.

CASE 3. **Focal Fits with Spreading Sensory and Motor Element, Loss of Consciousness with Aura of Dizziness**

A right posterior parietal brain wound soon after wounding caused slight left hemiparesis and reduction of passive movement sense in the left fingers and toes. Some years after wounding there was slight spatial disorientation in the left half visual field and some left finger agnosia. There was minimal weakness of the left arm and leg with slight loss of passive movement sense in the left fingers.

Fits.—**1.** Numbness passed up the left arm from the fingers, then into the left leg, starting with the toes and moving upwards, followed by jerking of the left hand at the wrist and the left foot soon afterwards. There was no loss of consciousness.

2. A sudden tingling in the fingers of the left hand passed rapidly up to the elbow and then disappeared.

3. Tonic rigidity and a numb feeling of the left abdominal wall was followed immediately by clonic jerking of this and of the cremasterics. There was no loss of consciousness.

4. There was a sudden dizziness and the patient had time to lie down before losing consciousness. There was pallor but no movements.

CASE 45. **Spreading Focal Sensory and Motor Attacks. Adversive Aura to Tonic Fit**

A left posterior frontal wound soon after wounding caused jargon aphasia and right hemiparesis with some loss to all forms of sensation on the right. Some years later there was still slight dysphasia and slight weakness and increased tone in the right hand. Stereognosis was reduced in this hand, as was two-point touch, and this reduction was also found on the right upper lip.

Fits.—**1.** The right hand suddenly went numb. This was followed in a few seconds by a jerking of the hand and the right eye-lid. The right side of the face felt intensely cold. Sometimes the lip also twitched at this stage. Speech was thick but there was apparently no dysphasia. Sometimes as the right hand started jerking, the right leg also twitched. There was no loss of consciousness.

2. The eyes seem forcibly turned to the right. The patient cried out, then lost consciousness, and a general tonic fit ensued without any clonic element.

CASE 37. **Spreading Focal Sensory and Motor Attacks sometimes Proceeding to Grand Mal**

A left frontal to posterior parietal brain wound soon after wounding caused right hemiparesis with right-sided sensory loss to all modalities and global dysphasia. Some years later there was a very slight spastic weakness of the right hand, but no definite sensory loss. Slight dysphasia occurred in emotional situations.

Fits.—**1.** A sudden numbness of the right hand spread up the arm to the shoulder, then the leg and jaw started jerking, and consciousness was lost with a generalized convulsion.

2. Jerking of the right face, and then both legs, was continuous for about four hours and then ceased abruptly. This was observed only in the early fits.

However, the march of events in the spread of an attack seems at times to jump the expected anatomical sequence as in Case 77 (above). The variation

which may occur in the Jacksonian march presumably depends on the continual changes in the setting of the motor cortex.

Multiple Forms of Aura in One Case

In some cases of small Rolandic wounds two or more types of fit may occur. A fit must originate in relatively normal cells adjacent to the traumatic lesion, and the appearance of more than one type of fit seems at first sight to indicate the development of more than one discharging focus around the scar. However, it may be due to different responses from the same focus as the intensity or some other quality of the discharge changes, just as the neurophysiologist can elicit a variety of motor response from a given cortical point by changing the conditions of the experiment (Liddell and Phillips, 1950).

These points are demonstrated in the following case, and in Cases 4 and 32 among others.

CASE 53. **Focal Fits with Varying Sensory and Clonic Motor Onset. Adversive Onset to Grand Mal Attack**

A left posterior parietal brain wound early after wounding caused a right lower quadrantic homonymous field defect. The right arm was weak and atonic with loss of the appreciation of passive movement. The right face was also weak. Some years after wounding the right quadrantic field defect remained together with slight reduction of passive movement sense and stereognosis in the right hand.

Fits.—**1.** Suddenly a spot as of reflected light appeared in front of the eyes, which was difficult to localize in the visual field. The right arm then felt as if it were moving below the elbow, and the triceps region felt as if the muscle were being torn, though this was not described as painful. There was no objective movement, nor loss of consciousness.

2. A sudden feeling of numbness in the right hand was followed immediately by twitching of the right hand, but no tonic movement.

3. A generalized convulsion started with adversive movements of the head to the left. During the generalized convulsion movements occurred more on the right than on the left side.

Epilepsia Partialis Continua

Partial continuous epilepsy seems to occupy a special position amongst the motor auras, particularly so far as the spread of the epileptic process is concerned. It has been pointed out that nothing comparable seems to occur in the sensory sphere. Moreover, it tends to occur mainly in the first few weeks after wounding when the patho-physiology of the cortex must be quite different from the more chronic condition of some years later. The tendency to continued clonic movement which neither spreads nor ceases would suggest perhaps the activity of a region of cortex relatively isolated so far as its afferent and transcortical connexions are concerned. The individual focal clonic attack—and for that matter the isolated grand mal attack also—is presumably terminated in such a positive manner that the discharging focus is rendered refractory for a considerable time. The following cases (and also No. 79) illustrate this type of attack.

CASE 33. **Partial Continuous Epilepsy of Foot**

A right frontal wound with a foreign body passing to the right occipital lobe subsequently became septic and caused death in three weeks. Soon after wounding there was marked left hemiparesis, stupor, and dysphasia. The right hand showed continual groping and grasping movements.

Fits.—Early after wounding there were clonic movements in the right foot and ankle, which passed up the leg, and then to the shoulder, the sternomastoids, and down to the triceps muscles, but no further. The movements were continued for 10 days uninterruptedly. In addition to this, during the period of continuous movement, there were occasional isolated twitches of the right face and thumb.

CASE 68. **Partial Continuous Epilepsy of Foot. Focal Adversive and Tonic Fits.**

A right fronto-parietal brain wound (through and through) soon after wounding caused left hemiplegia with reduced tone. Passive movement sense and light touch were abolished in the left hand and foot. Some years later there was a slight spastic hemiparesis, more marked in the arm than in the leg, but no sensory changes.

Fits.—**1.** Early after wounding rhythmic contractions of the medial plantar and posterior tibial and peroneal muscles of the left foot at a rate of about 6 per second were maintained uninterruptedly for four days. Movements were sudden isolated contractions with slower relaxation.

2. A feeling came over the patient that he had to look at the left hand. Then the eyes and the head started moving slowly round to the left. Consciousness was fully preserved, but he had to remain still till the forced turning ended " in a few minutes ". There was no clonic element.

" Focal status ", as it is sometimes called, should be sharply differentiated from generalized status epilepticus. The latter is a medical emergency calling for urgent treatment to arrest the attacks, which may otherwise rapidly exhaust the patient and lead to death. The former seems to incommode the patient little, and is, in fact, so resistant to the usual anticonvulsants that determined endeavours to end it by these means may do more harm than

good. A type of continuing focal discharge may occasionally be seen during a grand mal status. Here a continuous local clonic discharge occurs between each grand mal attack. However, the clinical site of discharge in this type of case is not constant, but flits from group to group of muscles, and the impression is gained that this represents a reduced continuation of the grand mal seizures, and that the physiological background of this and true partial continuous epilepsy is different. Cases 63 and 52 illustrate this.

CASE 63. **Status Epilepticus with Focal Clonic Movements between Fits. Focal, Clonic Attacks in Left Limbs**

A left parieto-occipital parasagittal brain wound early after wounding caused global dysphasia, dysgraphia, and dyslexia, with a right hemianopia and some defect in the left lower visual field also. Some years later there was receptive and expressive dysphasia which was much worse when the patient was emotionally upset. There was dyscalculia and dysgraphia, but he could read slowly and write accurately with correction. A right hemianopia with a left lower quadrant defect was also present.

Fits.—**1.** There was status epilepticus with generalized tonic stiffening but clonic movements mainly on the left side, though the head and neck were involved as well. In the intervals between the more generalized clonic movements there was a sort of intermittent partial continuous epilepsy, sometimes in the left hand, sometimes in the face—just a continuous clonic flickering of a few muscles.

2. A sudden twitching of the left face passed to the left arm with no tonic movement. Sometimes twitching began in the hand and sometimes in the left leg, and then passed to the arm and face. After this there was residual weakness in the left arm for half an hour or so.

3. The pattern of the fit was as in 1, but consciousness was then lost, and continuous clonic movements confined to the left side occurred with occasional brief spreads to the right arm also.

4. On one occasion only a sudden loss of speech was followed at once by complete motor loss with falling. There was no movement and no loss of consciousness.

CASE 52. **Generalized Grand Mal with Continuing Focal Clonic Movements between Consecutive Attacks**

A right frontal wound soon after wounding caused left facial weakness. Some years later there were no abnormalities in the central nervous system.

Fits.—**1.** There was occasional serial epilepsy with some hours' interval between each attack. Sometimes between attacks focal clonic movements would occur, shifting from the right face to the right arm or to the eyes. In these consciousness was preserved.

2. Generalized grand mal attacks occurred with no aura.

Methods of Arresting Focal Fits

It is often thought that a " busy " area of cortex is less likely to discharge spontaneously, and in this connexion it is interesting to note that patients sometimes discover a method by which application of a peripheral stimulus to the affected part will arrest a clonic motor attack. The manoeuvre usually involves forcible tension applied to the muscles involved or attempted strong voluntary movement of them. Cases 6, 66, and 69 illustrate this. Penfield and Kristiansen (1951) have observed in a case of focal status affecting one foot that electrical stimulation of the foot area of the motor cortex abolished the attack. Possibly the strong voluntary effort or stimulus described above has a similar effect in forcing through an afferent stimulus to a relatively isolated area of cortex. Indeed these phenomena may be considered as evidence in favour of the view that focal fits develop in areas of the cortex which have been deprived of some of their afferent connexions. No case was recorded where a sensory fit was so arrested, though patients did sometimes attempt this by rubbing or moving the affected part.

FURTHER DETAILS OF VARIETIES OF MOTOR AND SENSORY ATTACKS

Myoclonic Jerks and " Electric Shock " Sensations

The myoclonic jerk may also occur as a variety of motor aura, though it is infrequent in this series (Table XI). Such an attack seems similar to the normal start reflex, and in fact in one case it occurred as a local aura in one limb only, in response to sudden noise. It was, however, more than a simple " start ", as the movement would sometimes develop into a short clonic attack. This motor aura seems paralleled on the sensory side by the sudden feeling as of an electric shock. This may be purely sensory, or it may be associated with a few clonic jerks in the part affected (Table XI). The rapidity of the phenomenon and the fact that it may involve the whole of a limb almost instantaneously suggest that it may represent some " short circuiting " process in the central nervous system, by which pathways become momentarily available for discharge. The following two cases illustrate both the pure sensory shock and the mixed motor-sensory type. Case 77 above also brings this point out well.

CASE 18. **Focal " Electric Shock " Feelings possibly Spreading to Focal Clonic Movements and Grand Mal**

The patient received a right Rolandic wound. Some years later there was slight spasticity of the left upper

limb, with cortical sensory loss in the left hand, more marked on the ulnar than the radial border.

Fits.—1. A sudden feeling like an electric shock, which ran round to the back of the head, occurred in the left neck: nothing further.

2. A sudden brief feeling like an electric shock occurred simultaneously in the hand and foot: nothing further.

3. A sudden, stinging feeling like pins and needles in the left hand passed rapidly up to the shoulder. Then a similar feeling appeared in the left leg, which ran up the leg to the side, the abdomen, and then the loin. Twitching then began in the left face around the eye. A choking sensation occurred in the throat and consciousness was lost, and left-sided convulsions followed.

4. There was a sudden feeling of being unable to breathe properly. It was momentary only, and always occurred just at the time of falling asleep.

CASE 38. **Focal "Electric Shock Feeling" with Clonic Fits**

A right posterior parietal to frontal brain wound early after wounding caused left hemiplegia with sensory loss and homonymous hemianopia. Some years later there was a spastic hemiparesis, more marked in the arm than in the leg, and homonymous hemianopia. All forms of sensation were impaired, in the arm more than in the leg. This patient developed a schizophrenic reaction with paranoid features.

Fits. 1. A sudden feeling like an electric shock in the left arm passed rapidly up to the left face, when twitching of the face occurred. There was no further progress and no loss of consciousness.

2. The left hand was suddenly clenched; then clonic jerking occurred, followed by loss of consciousness and general convulsions.

Motor and Sensory Inhibitory Attacks

The inhibitory attacks require special mention. It has been suggested that they represent a discharge through a cortical inhibitory mechanism. As has been mentioned earlier, they tend to involve a larger area of the body than the focal clonic or positive sensory attacks, and this is in keeping with the physiological observation that stimulation of the suppressor areas in monkeys tends to produce widespread rather than localized motor inhibition. Both motor and sensory types of attack are observed, though in some cases the two seem closely associated in a given attack. Examples of motor inhibition are seen in Case 9 (above) which illustrates the widespread involvement first of the whole upper limb and rapidly thereafter of the leg also, and in Case 55 where both legs are involved.

CASE 55. **Focal Inhibitory and Focal Thermal Fits**

A right posterior parietal parasagittal wound soon after wounding caused weakness of both legs, the right more than the left. There was a slight sensory loss of cortical type in the right foot. The bladder was distended, and urination was difficult. Some years later there were no abnormal signs in the central nervous system.

Fits. 1. There was sudden loss of power in the legs but no sensory change was recalled. The patient fell, and there was a momentary loss of consciousness.

2. A queer feeling occurred in the epigastrium. Then came a hot, burning feeling in the left hand, which spread rapidly up the arm to the shoulder. The attack then ceased. The sensation was one of heat but was not painful.

A focal aura of numbness probably represents a sensory inhibitory attack. Though the subjects' powers of accurate description vary, there seems to be a well maintained differentiation of these types of aura from the more positive pins and needles or tingling. In Case 3 (above) the patient described quite separately a "numb feeling" in some attacks and a tingling feeling in others, the former having a distinctive negative quality. Again in Case 40, widespread "numbness" in the whole of one side is distinguished from "pins and needles", which have a more focal reference. This may also be distinguished from agnosia which is referred to later.

CASE 40. **Focal Sensory Attacks sometimes Inhibitory and sometimes "Positive" with Focal Motor Element**

A right fronto-temporal brain wound soon after wounding caused some weakness with marked sensory change in the left hand. Any stimulus to the hand caused a strange, spreading feeling of an unpleasant character. Pin-prick was appreciated but diffusely, and there was marked cortical sensory loss. Some years later the left hand was a little weak and awkward to use, and always felt colder than the right. However, two-point touch and passive movement sense were well preserved, though stereognosis was reduced. There was an upper quadrant left field defect.

Fits.—1. A sudden, giddy feeling with numbness down the whole of the left side was usually followed by local jerking of the left arm and leg.

2. A sudden pins-and-needles feeling in the left arm almost immediately became a severe, burning sensation, which was very painful. This passed up the left arm, and then involved the left trunk, and sometimes also the left leg. The sensation of heat passed in a few seconds, leaving an unpleasant cold feeling in the same situation.

In these cases motor or sensory inhibitions are separate, but in Case 22 the two appear together again with a wide involvement of the whole upper limb. While in Case 829 sensory inhibition leads on to motor, and the process spreads rapidly to the whole of one side.

CASE 22. **Sensory and Motor Focal Inhibitory Attacks**

A right Rolandic brain wound soon after wounding caused weakness with sensory change in the left hand. Light touch and pin-prick gave a tingling, widely radiating response; though touch was fairly well localized, passive movement sense was reduced, as were stereognosis and two-point touch. Some years later there was slight cortical sensory loss in the left hand, mainly on the ulnar border.

Fits.—The left hand suddenly felt dead and numb. There was no tingling associated with this; the sensation seemed to be a negative one. At the same time attempts to use the hand were unavailing, and no movement occurred.

CASE 829 (not in tables). **Focal Sensory and Motor Inhibitory Attacks followed by Focal Clonic Movements and sometimes by Loss of Consciousness**

A left frontal brain wound (Fig. 4) soon after wounding caused global aphasia, with some weakness of the right arm and loss of facility of movement. No sensory changes were found. Some years later there was still slight expressive dysphasia, especially when the patient was emotionally upset. There was a slight increase in tone in the right hand but no other abnormalities.

FIG. 4.—Skull tracing of Case 829.

Fits.—**1.** There was a sudden feeling in the right arm, difficult to describe, but as if the arm were weak and nothing could be felt in it. This was accompanied almost immediately by an actual loss of power, so that anything held in the hand would be dropped, and the arm would fall to the side. A few seconds later the leg would also be involved; first the feeling, then loss of power, so that the patient would fall to the right side. At this stage there were usually, but not always, a few clonic jerks of the right arm, and less so of the right leg. The attack then ceased.

2. As above, but on falling to the ground there was loss of consciousness with convulsions, involving mainly the right side.

Auras of Agnosia and Phantom Sensations

A further and most interesting example of sensory inhibition is provided by the auras of focal agnosia. Here patients describe the sudden feeling that some part of the body is no longer there, and they may look at the continuing physical reality of the part with surprise. Here again, the areas of the body involved are usually fairly large as in other inhibitory attacks. In Cases 10 and 36 (see above) the arm suddenly seemed to disappear, to be followed shortly by the leg. In Case 84 the attack involved half of the face and the arm and leg, while in Case 59 only the arm was involved and in Case 21 (above) only one half of the face. In these attacks, although power is preserved in the limb, there may be some disability and clumsiness of movement.

These attacks presumably represent a discharge affecting the body image mechanism in the posterior parietal lobe, and the disposition of wounds in such cases on the whole supports this localization. Contrasted with these negative phenomena, but still involving areas concerned with organization of the body image, are the auras of phantom sensation. In Case 58 the aura took the form of a highly organized phantom arm. In Case 76 the aura was more limited in extent involving a sensation of movement in fingers which were, in fact, still, while in Case 53 (see above) the aura was even more limited and bizarre.

CASE 58. **Focal Attack of Phantom Limb. Grand Mal with no Aura**

A left posterior parietal brain wound soon after wounding caused a right homonymous field defect with sensory loss in the right hand—reduced passive movement sense, two-point touch, and stereognosis. Pin-prick was appreciated, but was radiating and intense. The reflexes of the right arm and leg were increased compared with the left. Some years later there was a right homonymous lower quadrant field defect. Stationary objects would be missed from this field, though appreciated when moving. Localization of objects in the right field was also reduced. There was occasional attention defect in the somatic sensory sphere also with astereognosis in the right arm. Tone in the right limbs was slightly increased, and there were bilateral equivocal plantar responses.

Fits.—**1.** A sudden feeling occurred that the right arm was in a position elevated above the head with the hand clenched and the elbow semi-flexed. The patient looked up in this direction to find the hand was not there but by his side. The feeling might be so strong that he would, in bed, ask his wife to pull the arm down, though in fact it was still by his side.

Sometimes, but rarely, there is a slight feeling of pins and needles in the phantom arm in the raised position.

CASE 76. **Focal Fits of "Phantom Movement". Visual Aura with Sense of Familiarity followed by Occasional Loss of Consciousness**

A right temporo-parietal brain wound soon after wounding caused left hemiplegia with left sensory loss to all modalities and hemianopia.

Some years later there was a left hemiparesis, more marked in the arm than in the leg. There was reduced appreciation to light touch and passive movement sense in the left hand. Hot and cold were appreciated but pin-prick was changed and radiating. These changes were present but less marked in the leg. There was a

complete left homonymous hemianopia and also some difficulty in appreciating spatial relations.

Fits.—1. A sudden feeling occurred as if the fingers in the left hand were moving, clenching, and unclenching, though in fact no movement was occurring.

2. As above, then there was actual stiffening of the hand in a clenched position with some flexion at the elbow, followed by clonic movements at the elbow.

3. The above phenomena were followed by a curtain suddenly appearing over the normal half visual field. This was accompanied by a picture of something which could not be described, but was always the same. This might proceed to complete loss of consciousness, but without further motor phenomena.

Painful and Thermal Auras

Two other sensory auras remain to be mentioned, both of them of special interest to cerebral physiology. These are concerned with sensations of pain and temperature.

In four cases pain was mentioned as some part of an aura. In Case 20 (see above) this was a severe and intensely unpleasant, rather indefinable sensation which occurred at the onset and was the main part of the aura. In Case 7 (below) pain was more clearly defined and described as like a painful spasm, though no actual muscular spasm occurred, while in Case 73 pain was actually associated with tonic spasm. In Case 74 pain followed a clonic motor aura and was again severe and hard to describe—it showed a spread from the abdomen to the thorax and then to the neck on one side—following the march of the preceding clonic movement.

CASE 7. **Focal Aura of Pain with Clonic Element**

A right anterior parietal parasagittal brain wound soon after wounding caused complete motor aphasia and left hemiplegia with some sensory loss in the left hand. Some years later there was a spastic weakness of the left arm and less so of the left leg. There was some hyperpathia in the left hand, and joint sense and two-point touch were reduced.

Fits.—**1.** A painful feeling as of cramp occurred in the left face, though there was no noticeable stiffening or movement. This was followed by painless twitching of the face. Directly after this there was twitching of the left leg, and then of the shoulder but not of the arm, with no further spread.

2. As in 1 but afterwards there was spread of movement to the leg, consciousness was lost, and the patient fell, but no generalized convulsion occurred.

3. There was sudden stiffening of the left leg with painful cramp, then clonic movements of the leg, but no further spread.

No fewer than 11 patients mentioned definite thermal sensations as part of an aura. Of these nine had sensations of heat or warmth, at times so intense as to be very painful. Two had feelings of cold, and in one temperature change was so intense that it was impossible for the patient to decide whether it was hot or cold. In 10 cases auras were referred to the arm, and in one the face was involved. Cases 4, 8, 21, 39, 40, 54, and 55, have already been referred to above. The following three cases also illustrate this aura :

CASE 30. **Focal Sensory Attacks, Tingling and Thermal. Adversive Aura to Grand Mal**

A right parietal wound soon after wounding caused slight left hemiparesis with sensory loss in the hand and hemianopia. Some years later there was no discernible motor abnormality but some reduction of temperature appreciation in the left arm and leg and the hemianopia persisted.

Fits.—**1.** Tingling in the left hand passed up the arm to the face, and then involved the leg. This was followed almost immediately by a feeling of intense heat running up the arm and at the same time in the leg. Then the attack ceased.

2. Sudden pins and needles occurred in the left face—nothing more.

3. The head and eyes were slowly turned to the left, consciousness was then lost, and a grand mal convulsion ensued.

CASE 42. **Focal Fits with Aphasia, Thermal, Sensory and Clonic Aura in Right Hand and Possible Loss of Consciousness**

A left fronto-temporal brain wound some years after wounding caused a right homonymous lower quadrantic field defect, dysphasia, dyslexia, and dysgraphia, with loss of dexterity in movements of the right hand, though little actual weakness.

Fits.—**1.** There was sudden loss of speech for a few seconds, then loss of consciousness with a generalized convulsion.

2. Sometimes after the speechlessness and before loss of consciousness a hot feeling occurred in the right hand which spread up the arm to the shoulder and was followed at once by clonic movements in the hand and forearm.

3. Sometimes attacks occurred as in 2, but there was loss of consciousness after the clonic movement.

CASE 44. **Thermal, Sensory, and Clonic Focal Fits. Grand Mal with Aura of Focal Clonic Movements**

A left frontal to temporal brain wound was sustained, one foreign body having passed down to the temporal fossa. Early after wounding there was aphasia, motor more than sensory, with right hemiplegia. Some years

later the patient still had marked motor aphasia, and the right hand showed ataxia, but with little actual weakness. The leg was hypertonic, but power and movements were well preserved. He could now draw and write well with his left hand. On the sensory side, pin-prick and temperature appreciation were reduced, though not abolished, in the right hand. Two-point touch and stereognosis were also reduced in this limb. The leg showed no sensory defect.

Fits.—**1.** A sudden burning sensation occurred in the right hand running up the arm. This feeling was intense and unpleasant, and the patient rushed to put the arm under a cold water tap as this helped.

2. Sometimes this sensation was followed immediately by local jerking of the right hand and arm.

3. Sudden local twitching of the fourth and fifth fingers of the right hand, which travelled up the arm, occurred. Consciousness was lost and a generalized convulsion ensued.

It may be seen from these examples that thermal sensations can occur at the onset of an aura or at the end. Although a feeling of heat is the usual form, in two cases hot and cold feelings occurred in the same attack. In two also there was a change of aura from pins and needles to heat during an attack. This group also shows some of the rare cases in which a motor aura proceeds to a sensory, and both clonic and tonic movement immediately preceding the temperature changes have been recorded. The anatomical implications from the study of these cases is considered later.

ANATOMICAL CONSIDERATIONS

Extent of Wound and Clinical Deficit in Relation to Fit

The site of wounding and the type of sensori-motor deficit clearly play an important part in determining the type of fit which will occur spontaneously. An abnormal discharge can only act through a functioning cell so that a fit can only originate in, say, the motor cortex if a part at least of that cortex is functioning.

In this connexion the occurrence of clonic focal auras appears to be far more frequent in the small Rolandic wounds where permanent sensori-motor deficits are not extensive than in those cases where wounds are larger and permanent severe hemiplegias result. This lends some support to the general view, derived in part from experimental studies of the fit pattern after cortical ablation, that the cortex is specifically concerned with clonic movements. In Table VII cases with severe residual hemiplegia are separated from those with less extensive signs, and the more frequent occurrence of clonic focal seizures and their onset relatively early (under one month) after wounding in the latter group is clearly shown. Further, among the 52 cases with focal clonic fits, there were 14 which had *only* focal attacks on a five-year follow up, while the remaining 38 cases had also developed general convulsions on one or more occasions. Of the 14 cases with focal clonic fits alone (at the five-year follow-up) only three had a permanent severe hemiplegia. The remaining 11 had less paralysis, and in eight of these 11 cases the focal fits began within a month of wounding.

It seems therefore that the focal fits which remain focal are more likely to be those which follow the less severe wounds of the sensori-motor cortex, and these are also more likely to develop very soon after wounding.

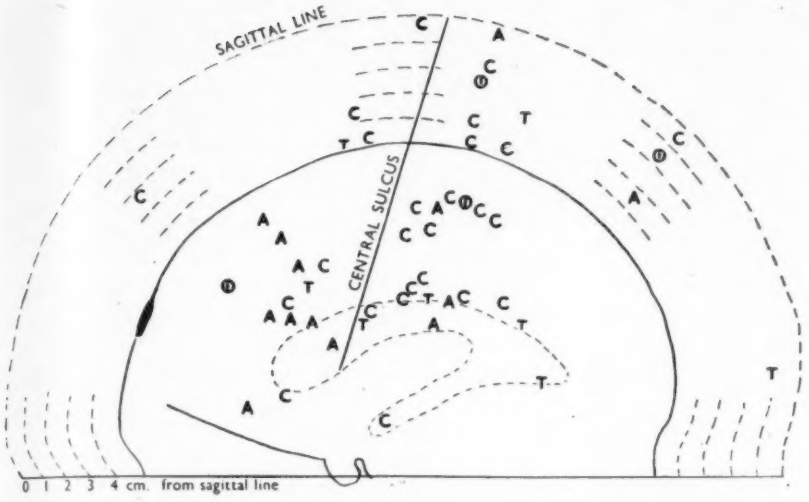
A great variety of sensory and motor auras is observed in the small wounds included in this series, and we can conclude that many of these can only appear when certain parts of the sensori-motor cortex are intact.

Many of the cases of hemiplegia in groups 6 and 7 of Table IX must have had most of both the sensory and motor cortex destroyed. In contrast to the smaller wounds these cases show few in which there are focal clonic motor auras, while the tonic type of motor aura is the more common (Table X). Whether this tonic discharge originates in other parts of the cortex, such as the pre-motor region or in deeper motor centres, cannot, however, be determined from this material, though several of the adversive auras with their strongly tonic setting clearly originate from the pre-motor region (Fig. 5).

Another and most striking feature of the hemiplegic cases is that sensory auras are very uncommon (Table X). It seems reasonable to associate this with disappearance of the sensory cortex, and if this is a correct assumption, as in most of these cases the thalamus cannot have been directly injured, it may be concluded that sensory discharges require integrity of the post-central gyrus for them to occur, or at any rate for them to be appreciated in consciousness.

Site of Wound and Type of Fit

The effects of electrical stimulation of the motor cortex suggest that the pre-central gyrus is the site of origin for most cases of focal clonic fits, but we have little information as to whether the spontaneous occurrences of these focal fits represent an irritative or a release phenomenon. The common appearance of a considerable latent interval between injury and the onset of fits in traumatic epilepsy is perhaps more in favour of an area of cortex gradu-



FIGS. 5 and 6.—Charts to show the site of skull penetration of a series of wounds causing focal motor (Fig. 5) and sensory (Fig. 6) auras. Cases of severe hemiplegia are excluded. Wounds lying within 5 cm. of the sagittal line are charted in the halo. Method of charting is as described by Russell (1947).

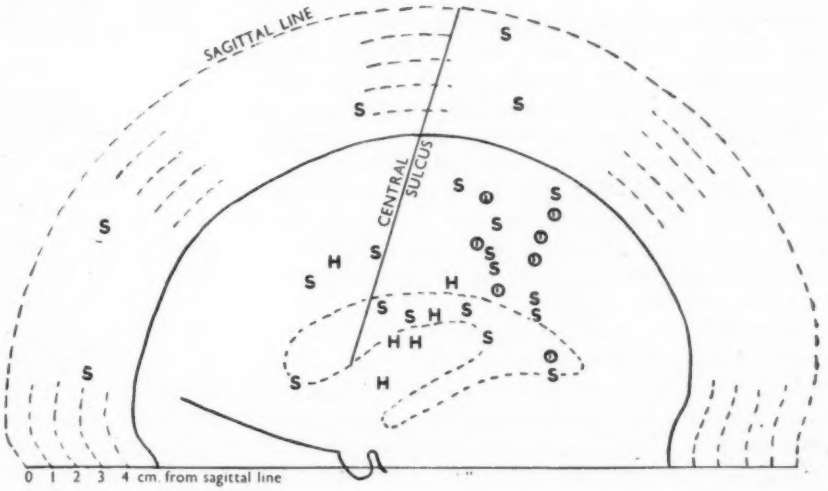
Types of aura: A = adversive, C = clonic, T = tonic, (I) = inhibitory (motor in Fig. 5, sensory in Fig. 6), S = sensory positive, H = aura of heat or cold.

ally becoming over-active through absence of control or through physical isolation, and with this in mind it is by no means impossible that damage to the *sensory* cortex plays an important part in the development of focal clonic *motor* discharges. In Fig. 5 the site of penetration of wounds (not causing severe hemiplegia) but which were followed by motor fits is charted, and it is evident that most of these points for cases with clonic fits lie behind the central sulcus. From this it is at least evident that the post-central gyrus is injured in most cases of focal clonic fits, an observation which is, in general, confirmed by reference to individual cases in Table IX.

Adversive attacks have already been referred to as often originating around posterior frontal wounds (Fig. 5). It may be noted, however, that they may occur in cases of severe hemiplegia and thus seem to be independent of the Rolandic region.

The anatomical aspects of the various sensory auras present difficulties. The main somatic sensory projection reaches the post-central gyrus via the thalamus, and circuits back to the thalamus. But what then? Presumably there is a complex "development" of what arrives at the cortex in the adjacent more posterior parietal lobe, but at what stage does the sensation result in the mental recognition and localization of a sensation?

The position of penetration of small wounds causing positive or negative (inhibitory) sensations is charted in Fig. 6. These wounds are, in general, a little more posterior than those which cause



clonic focal fits, but we can say little more. Both types of sensory aura often spread to focal clonic movements (Table XI), and this probably provides the best evidence that the post-central gyrus is concerned, but from Table XI it is seen that all forms of sensory aura may spread to clonic movements except the phantom and agnosia sensation.

Most of the sensory auras described are so precisely localized that the body image mechanism must be intact even though cortical sensation, by which it is largely "fed", is disrupted. This mechanism correlates the somatic sensory and visual plan of the body in relation to the environment, and

the several cases with auras of agnosia have sustained injury involving the posterior parietal lobe, which is the generally accepted anatomical site for this function. Case 59 is a good example, and the subject will be considered again in the next part of this study.

The description of an aura of agnosia indicates the disappearance of a sense of body existence and position which is at other times preserved. Being inhibitory without any positive accompaniments, an aura of agnosia probably originates in the midst of the body image mechanism. In three instances the sensation was self-limited (Table IX), in one it passed to a visual aura, in one to an inhibitory motor episode, and in one to a tonic adversive fit, but in no instance did it pass to a positive sensory experience.

A phantom sensation suggests a positive stimulus to an intact body image mechanism, but in no instance was there a record of phantom spreading to agnosia or the reverse. Indeed, neither of these phenomena was associated with other sensory attacks of any kind.

The four cases which show an aura of local pain are of great interest. Two of them (Nos. 7 and 20) had small wounds near the Rolandic fissure with a part of the sensory cortex clearly intact, and may thus confirm the recent evidence that the sensory cortex may, in some cases, play an important part in the appreciation of pain (Marshall, 1951).

In both these cases the pain occurred as the initial part of an aura. In the other two cases (Nos. 73 and 74), the injury was more extensive but was so situated that a part of the sensory cortex was also probably intact.

Sensations of heat or cold form a remarkable group, and must be studied from the point of view that they might throw light on the cerebral mechanisms concerned with temperature sense, at present little known. The 11 cases concerned were wounds associated with little sensory loss or motor disorder, and there is certainly no evidence of deep cerebral injury being a feature of these cases. The site of skull penetration in six of these, where the wound was relatively small, is shown in Fig. 6. From Table XI certain special associations emerge. In the first place two cases with a positive sensory aura spread to a thermal sensation, and these provided the only examples of spread from one type of sensory aura to another. The other remarkable feature is that thermal sensations formed four out of the only six examples of motor to sensory spread. These sensations therefore of hot and cold seem to form a unique link between clonic movements and pins and needles, or more strictly between the motor and sensory cortex from which these auras respectively originate. The apparent grouping of the wounds around the lateral fissure raises the possibility that the so-called " secondary sensory area " is concerned. The tendency for these auras to spread to other sensory auras and to be initiated by motor auras would also suggest a less discriminative and more " primitive " level of firing, which might also be in keeping with what is known of these secondary areas.

The inhibitory auras are represented by paralysis, numbness, and agnosia. The site of wounding in some of these cases is shown in Figs. 5 and 6, but this indicates no obvious anatomical distinction from the site of wounding in cases with positive sensory and motor attacks.

Table XI indicates that an aura of focal paralysis never passed to another kind of aura, but was either self-limited or proceeded to loss of consciousness. Auras of numbness on three occasions, and an aura of agnosia in one case did pass to focal paralysis. These were the only examples of a sensory aura proceeding to an inhibitory motor episode, and they clearly suggest a linkage between these various inhibitory forms of attack.

DISCUSSION

The present study is concerned with the analysis of the various features observed in spontaneously occurring focal fits following wounds of the sensorimotor cortex. Aphasic features are not considered here, as they are studied in a later paper. The observations reported are in some ways complementary to the careful observations on cortical stimulation by Foerster, Penfield, and others during the past half century. The variety of sensation, movement, and inhibition is as great in the spontaneously occurring fit as in those obtained by cortical stimulation, while the spread of the cortical discharge from one sensation to another may be more vividly described than can be hoped for by the patient on the operating table. Not that these spontaneously occurring epileptic discharges can be interpreted with any confidence, but their variety provides many arresting glimpses into the complexity of cerebral function.

Considering only marked and clearly defined differences in type of aura, it would seem (Table X) that at least five motor and seven sensory varieties can occur. On the motor side, although adversive attacks are to some extent only special examples of tonic movements, they form such a clear cut clinical entity, as well as often having a distinctive anatomical background, that they are considered as a separate group. On the sensory side, tingling and

pins and needles are considered together because their distinction was often difficult for the patient. However, in some cases their different qualities were clearly appreciated, and it is possible that they should be regarded as two varieties of response. Indeed, if we consider the minor differences in both the sensory and motor content and in the whole setting and sequence of the attacks—features which do, in fact, give them an individual " flavour "—then the impression of great variety of response from the sensori-motor cortex is enhanced. This is in keeping with Penfield and Kristiansen's (1951) findings from stimulation of the human cortex in which they mention no less than 21 different kinds of sensory aura. The occurrence of auras of pain, heat, or cold, in cases of small cortical wounds, is of special interest from the point of view of localization of function in the brain. The rarity of painful auras in our series is also reflected in results from cortical stimulation (Penfield and Kristiansen). Only two were recorded in all their series, and as these were usually associated with motor responses, they tentatively explained them as simply secondary results of muscle spasm. We have given reasons above for suggesting that this cannot be the explanation in all our own cases. Moreover, Lewin and Phillips (1952), among others, have recently reproduced the severe pain of an epileptic aura by stimulating electrically the post-central gyrus under local anaesthesia (Case 20). They have also abolished or greatly modified spontaneously occurring pain of an intractable type by excising the area of post-central gyrus from which the pain was produced on stimulation. So far as thermal auras are concerned, although they occurred in four cases as part of a spontaneous fit in Penfield's series, in no case were they reproduced by cortical stimulation. This might be taken as an argument in favour of their non-cortical origin. However, in all our cases showing these auras, the evidence for a cortical origin of the fits is quite as strong as in the examples of the many other forms of sensory and motor attacks which we have recorded. The patients with a thermal aura had often been wounded near the lateral fissure and the possible significance of this has already been considered.

Excitation and inhibition both on the motor and sensory side appear to be clearly represented in the cortical responses we have studied, and the way in which the very various auras may spread one to another has proved of special interest.

Although broad anatomical divisions of the sensori-motor cortex do appear to be maintained for the different qualities and bodily sites of epileptic response, our findings do not suggest that these can be rigidly determined by this form of study. The impression is one of flexibility of cortical response. Such a view is in agreement both with the general trend of present neurophysiological work, and with the results of cortical stimulation in man where pre- or post-central sites may each give rise to sensory or motor responses.

SUMMARY

Eighty-five cases of focal motor and somatic sensory fits are studied.

Five motor and seven sensory varieties are distinguished.

The relation of the site of injury, and the sensori-motor deficit to these auras is considered.

The direction of spread from one type of aura to another is considered.

The anatomical and physiological implications are discussed.

Acknowledgments will be made in a later section of this study.

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DEPOSITS OF FLUORESCENT ACID-FAST PRODUCTS IN THE NERVOUS SYSTEM AND SKELETAL MUSCLES OF ADULT RATS WITH CHRONIC VITAMIN-E DEFICIENCY

BY

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Since 1940 there have appeared several reports on neuromuscular lesions in adult rats in experimental vitamin-E deficiency. It is apparent that side by side with changing concepts of vitamin E and the effects of its deficiency in general, a considerable change in the evaluation of the neuromuscular lesions in particular has taken place.

Since the occurrence of neural lesions in experimental vitamin-E deficiency has been seriously doubted, and the earlier work of Einarson and Ringsted (1938) on this subject has been strongly criticized by some leading authorities on vitamin E, I have found it absolutely necessary to reinvestigate the matter, with special reference to the changes of the nerve cells, in particular the cell change I have called "cellular lipodystrophy". Two of my recent works on this subject have already been published (Einarson, 1952a and b), and the present paper is the third in the new series.

Ringsted (1935) reported certain neuromuscular disturbances in adult rats that had been kept on a vitamin-E deficient diet for a long period (months). This observation formed the basis of our comprehensive investigation of the whole neuromuscular syndrome and its pathogenesis, and three years later we published our monograph on the effect of chronic vitamin-E deficiency on the nervous system and the skeletal musculature in adult rats (Einarson and Ringsted, 1938). In the following years this publication was supplemented by some brief papers on the subject (Ringsted and Einarson, 1939; Einarson and Ringsted, 1939; Einarson, 1941), and the problem has been further dealt with in some of my later work on the structural changes of nerve cells (Einarson, 1945; Einarson and Lorentzen, 1946; Einarson, 1949).

A very conspicuous and important feature of the histological changes in vitamin E-deficient adult rats is the regular occurrence of peculiar lipoid products in the nervous system, as originally reported and illustrated by Einarson and Ringsted (1938). These products are insoluble in alcohol, stain reddish-orange with fat stains, and give an intense orthochromatic colour (e.g., a pure blue or green) with basic aniline dyes, but they are left completely unstained by gallocyanin-chromalum (Einarson and Ringsted, 1938; Einarson, 1941, 1949, 1952). The facts, to be demonstrated in this paper, that the products in question are also fluorescent on ultraviolet irradiation and acid-fast when stained by carbol fuchsin add some additional important characteristics. The products mentioned are regularly absent in normal rats or controls receiving protective doses of vitamin E.

This paper will deal mainly with the structural appearance and distribution of these fluorescent, acid-fast deposits in the nervous system and skeletal muscles of vitamin E-deficient adult rats. However, I find it appropriate first to give a brief account of the clinical symptoms displayed by the rats.

The Clinical Picture

The clinical picture bears the unmistakable stamp of a neuropathic syndrome including hyperkinesia, tremors, some transient muscular rigidity, increasing hypaesthesia and hypalgesia, prominent ataxia and dysmetria, progressive paralyses and muscular atrophies which, in the final stage, show a marked symmetrical distribution. Finally the animals become exhausted and mentally very slow or sluggish. Also there occurs a symmetrical loss of hair and other trophic disturbances in the skin (atrophy and ulcerations), and finally a lowered circulation in the front and hind paws, the skin becoming cooler than usual and cyanotic. Incontinence of the bladder develops in most of the animals.

In our detailed description of the clinical picture we divided its development into four stages, but it

will not be further described in this paper. I shall merely add that the whole syndrome is an extremely chronic one. Its onset is insidious after many months on the experimental diet, and it proceeds very slowly ; from its first appearance it takes six to 15 months to develop completely. The neuromuscular disturbances mostly begin caudally and progress towards the head, affecting the front and hind legs and hind quarters in a remarkably symmetrical manner. The mentality and general thriving of the animals are not essentially affected until the end of the third or the beginning of the fourth stages. Very small daily doses of vitamin E will prevent the appearance of the disease, but even large doses fail to cure manifest disturbances, and vitamin E arrests the development of the disturbances only if given very early in the disease.

The whole clinical picture as summarized above deviates rather sharply from the paralysis in the young suckling rats described by Evans and Burr (1928), or the nutritional muscular dystrophy in guinea-pigs and rabbits reported by Goettsch and Pappenheimer (1931) ; both these are conditions of primary myopathy probably without neural lesions. In the sucklings the paralysis has an acute onset appearing as a sudden calamity towards the end of the lactation period, on about the twentieth to the twenty-fifth day of life, affecting mainly the musculature of the body wall and the posterior extremities in a diffuse manner. Some of the paralyzed sucklings recover spontaneously and completely, others recover with permanent paralyses, and others die without any premonitory symptoms. In the guinea-pigs and rabbits the disease also has an acute onset and a comparatively rapid course, the result being widely distributed changes of a severe muscular dystrophy, a condition cured by vitamin E. We have repeatedly emphasized these differences from the clinical syndrome in the adult rats. Besides the clinical difference, the deviations of the muscle changes in the suckling rats, the guinea-pigs, and rabbits from the picture of the muscle changes in the adult rats have been clearly emphasized by Demole (1939), Demole and Pfaltz (1940), and Mackenzie, Mackenzie, and McCollum (1940).

Thus, the clinical picture displayed by adult and old rats that have been kept on a vitamin-E deficient diet for a long time is by no means confined to the symptoms and course of a simple or uncomplicated myopathy, although it includes some essential myogenic lesions (phase II). On the contrary it bears the unmistakable stamp of disturbances of the nervous system, and, in my opinion, the completely negative response to vitamin-E therapy clearly demonstrates that early, irreversible neural lesions must be involved in the disease. As a matter of fact my histological examinations have again confirmed this point of view so as to leave no room for doubt.

Before giving an account of the histological changes, in particular the structural appearance of the fluorescent, acid-fast deposits mentioned above, I must preface some remarks on technique.

Technique

For the demonstration of fluorescent substances the large fluorescence apparatus " lux U.V." of Reichert was used. The source of light is the lux U.V. mercury high pressure burner, and the equipment of light filters consists of the well known Reichert combination, i.e., a chamber with copper sulphate solution as a red blocking filter, two ultra-violet filters (nos. 8079 and 8080), and a matt-white filter (no. 8078) for microscopy with the usual visible light.

The material was fixed in formalin or formalin vapour and either examined as frozen sections mounted in water or glycerine, or it was embedded in paraffin and the sections mounted in non-fluorescent immersion oil (Reichert), or in pure liquid paraffin which does not cause any disturbing fluorescence even after prolonged irradiation. In every case the sections were mounted on Reichert's non-fluorescent slides (U.V.-glass), which the filtered ultra-violet light easily penetrates.

It is noteworthy that before examining the sections in the fluorescence apparatus they may be stained with gallocyanin-chromalum (*p*H 1·64) if wanted, since this staining, in spite of the chromalum in the solution, weakens only to a minimum degree the primary fluorescence of the deposits. Of course the sections must be thoroughly washed in water before examination in the fluorescence apparatus. This makes it possible to examine the same nerve cell and compare its structural changes alternately in ultra-violet and visible light (Figs. 3, 6, 7). In thicker sections (10–20 μ) the stained Nissl substance may partly conceal the fluorescent deposits, but otherwise the gallocyanin-chromalum staining does not essentially interfere with the fluorescence of these deposits. This circumstance once again demonstrates the high degree of selectivity of the gallocyanin-chromalum staining. By any other of the usually applied staining methods for basophilic cell structures (e.g., the various haematoxylin methods, basic aniline dyes) the primary fluorescence of the products in question is totally lost.

For the demonstration of acid fastness the following procedure was adopted :—(1) Staining of paraffin sections in Ziehl-Neelsen's carbol fuchsin for two hours at 60° C. followed by washing in water ; (2) decolorization in 3% hydrochloric acid-alcohol (i.e., 3 ml. concentrated (37·5%) HCl to 97 ml. 70% alcohol) for 15 minutes to one hour ; (3) after washing in running tap water for a few minutes the slides are placed in distilled water ; (4) counterstaining with gallocyanin-chromalum (*p*H 1·64) for 48 hours at room temperature ; (5) washing

in distilled water, dehydration, clearing, and mounting as usual.

Acid-fast deposits stain an intense red, while nuclear chromatin, nucleoli, and the Nissl substance appear in the usual blue (Figs. A, B, C, D, E). On account of its exquisite progressivity and selectivity the counter-staining with gallocyanin-chromalum, a stoicheiometrical staining reaction for nucleic acids, is superior to any other method for staining basophilic cell structures known to me. It leaves the red staining of the acid-fast products completely unaffected. For the theory and practice of the gallocyanin-chromalum staining, I refer to my recent paper on this subject (Einarson, 1951). My evaluation of the degree of basophilia of the nerve cells (hyperchromasia, chromophoby, chromophily) is exclusively based on this staining method.

The Neuromuscular Lesions

The picture of the histological changes of the vitamin E-deficient adult rats clearly discloses the fact that the disease is due to a combination of neurogenic and myogenic lesions as originally maintained by Einarson and Ringsted (1938, 1939). The muscle changes in particular consist in a late atrophy of spinal origin superimposed on an early muscular dystrophy. The whole complex of neuromuscular lesions in adult rats may be subdivided into the following separate phases according to the site and sequence of their development, although some overlapping in time naturally takes place.

Phase I.—In phase I there is degeneration of the dorsal roots and posterior fasciculi of the spinal cord. As a rule, the process begins in the lumbosacral part of the spinal cord, and gradually progressing towards the head it often involves the cervical segments and even extends into the medulla oblongata. At the lumbosacral levels the entire posterior funiculus is mostly involved, while the lesion, when traced in the direction of the head, gradually becomes more restricted to the fasciculus gracilis, sometimes extending as far as the nucleus gracilis.

Histologically the changes consist of a distinct demyelinization and subsequent fragmentation and reduction of axons. The glial reactions are usually somewhat variable. Mostly, there is a rather marked increase in glial fibres in the demyelinized areas, within which scattered hypertrophic astrocytes are visible. Sometimes the demyelinized areas show a somewhat porous, spongy appearance traversed by the meshwork of glial fibres. As a rule, the histological changes are most marked in the fasciculus gracilis. Numerous scavenger cells, containing abundant normal lipoid breakdown products, staining a brilliant red with scarlet R, are seen, and the peculiar deposits insoluble in alcohol, showing marked affinity for basic aniline dyes and staining reddish-orange with scarlet R, are very characteristic. These products are also characterized by their acid fastness when stained by Ziehl-Neelsen's carbol fuchsin according to the procedure described above, and by their bright yellow primary fluorescence on ultra-violet irradiation. These products occur in gliogenous scavenger cells and other phagocytes, in or about astrocytes and oligodendrocytes, and in the walls of the blood vessels within the degenerated areas. They are invariably most abundant and closely packed in the fasciculus gracilis just where the degeneration is most marked (Figs. A and B).

Phase II.—In phase II there is myogenic atrophy of the skeletal muscles, especially pronounced in the hind legs and hind quarters. It begins, as a rule, in the adductors of the thigh, progressively involving more muscles of the posterior extremities as well as the muscles of the hip joint, the lumbar and abdominal regions. Sometimes the anterior extremities are also involved to some extent.

Histologically the muscle changes resemble those of progressive muscular dystrophy. The atrophy is diffuse, with normal, atrophic, and some hypertrophic muscle fibres being irregularly scattered between each other. Migration of nuclei into the muscle fibres is frequently observed, and in longitudinal sections long rows of such nuclei may be seen lying centrally in the muscle fibres. Longitudinal splitting is a constant phenomenon, and hypertrophic muscle fibres may be seen split up into several smaller fibres of varying size. Further, there is a globular fragmentation and disintegration of individual muscle fibres with an increase in hyperchromatic and pyknotic nuclei. Also fibres rich in sarcoplasm, showing signs of vacuolar degeneration, may be seen. Even at this stage of the disease the acid-fast fluorescent products are invariably present in the muscles, first practically confined to the endomysium in which many histiocytes may be filled with them. Later, as they gradually increase in number, they may also be seen lying inside the muscle fibres themselves (Figs. 1 and 2). Sometimes there is an increase of interstitial connective tissue and fat. These dystrophic changes develop rather slowly and mildly compared with the acute, severe, and histologically different muscle changes of the young suckling rats or the guinea-pigs and rabbits.

Thus, dystrophic muscle changes appear at the end of the first or early in the second clinical stage before any changes of the anterior horn cells can be seen. Phase II proceeds by degrees to the next phase (Einarson and Ringsted, 1939).

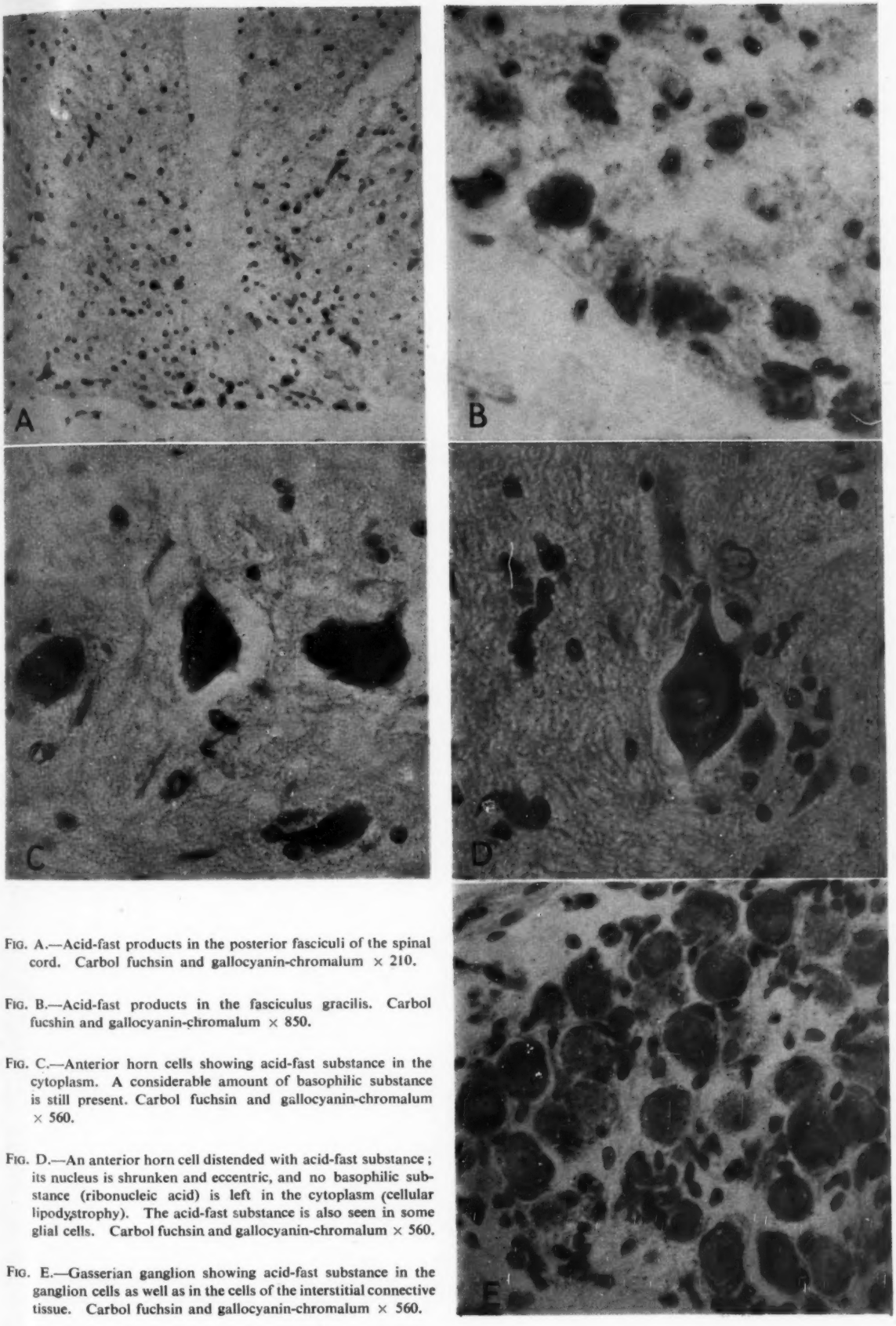

FIG. A.—Acid-fast products in the posterior fasciculi of the spinal cord. Carbol fuchsin and gallocyanin-chromalum × 210.

FIG. B.—Acid-fast products in the fasciculus gracilis. Carbol fucshin and gallocyanin-chromalum × 850.

FIG. C.—Anterior horn cells showing acid-fast substance in the cytoplasm. A considerable amount of basophilic substance is still present. Carbol fuchsin and gallocyanin-chromalum × 560.

FIG. D.—An anterior horn cell distended with acid-fast substance; its nucleus is shrunken and eccentric, and no basophilic substance (ribonucleic acid) is left in the cytoplasm (cellular lipodystrophy). The acid-fast substance is also seen in some glial cells. Carbol fuchsin and gallocyanin-chromalum × 560.

FIG. E.—Gasserian ganglion showing acid-fast substance in the ganglion cells as well as in the cells of the interstitial connective tissue. Carbol fuchsin and gallocyanin-chromalum × 560.

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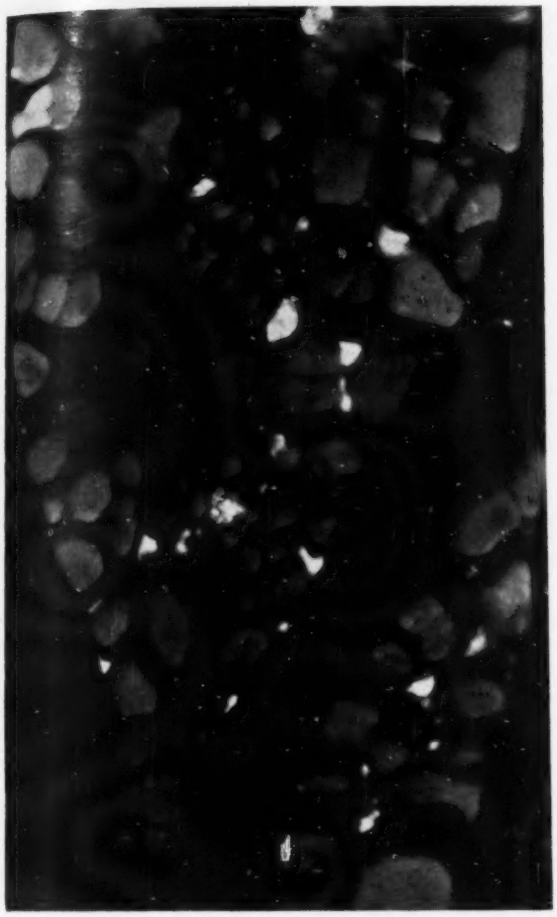


FIG. 1.—Transverse section of the adductor of the thigh showing fluorescent products in muscle fibres and histiocytes of the endomysium and patches of markedly atrophic, less atrophic, and normal muscle fibres. Unstained section. Reichert's "lux U.V." × 415.

Phase III.—In phase III there are slowly developing changes of the visceral and somatic motor and sensory cells of the spinal cord and brain stem. As a rule the cell changes first appear in the lumbar and sacral parts of the cord, and proceeding towards the head they gradually involve the whole spinal cord and brain stem. As the changes progressively involve more parts of the nervous system, and the number of nerve cells affected increases, the changes in each individual cell likewise become more marked. Although the visceral as well as the big motor cells, in particular the anterior horn cells, usually show the most pronounced changes, the cells of the posterior horns, the sensory nuclei of the brain stem, the spinal and cranial ganglion cells are also distinctly affected. It is of special interest to point out the early appearance and marked intensity of the cell changes in the intermediary, visceral columns of the spinal cord (Figs. 3 and 4), a feature particularly emphasized and illustrated by Einarson (1941). Exactly the same applies to the visceral nuclei of the brain stem, e.g., the dorsal motor nucleus of the vagus.

The cell changes referred to are somewhat variable, although they mostly pass through several consecutive structural stages. From the usual condition of normal staining the nerve cells pass through stages of hyperchromasia and chromophoby (reduced basophily) followed by stages of markedly increasing basophily leading to extreme chromophily and cell sclerosis. Gradually they lose their intense staining and end in irreparable cell atrophy with more or less corkscrew-shaped dendrites. At any of these stages the acid-fast fluorescent products may appear in the cytoplasm, often as an early structural sign in otherwise normal-looking cells. From a small cytoplasmic deposit the products gradually increase until the majority of the cells, while becoming chromophilic and atrophic, finally become more or less filled with them, while there is a simultaneous disappearance of the Nissl substance. This cytoplasmic change is accompanied by eccentric displacement, hyperchromatosis, and shrinkage of the nucleus. Thus, the nucleic acids of the cytoplasm are gradually replaced by the acid-fast fluorescent products, many cells showing mere

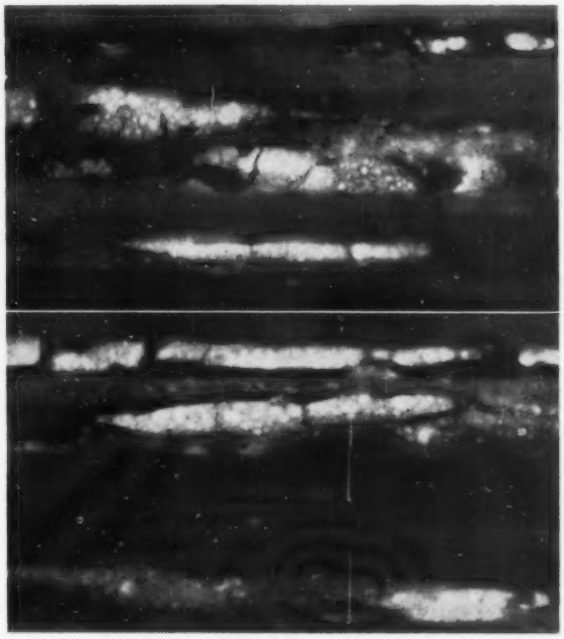
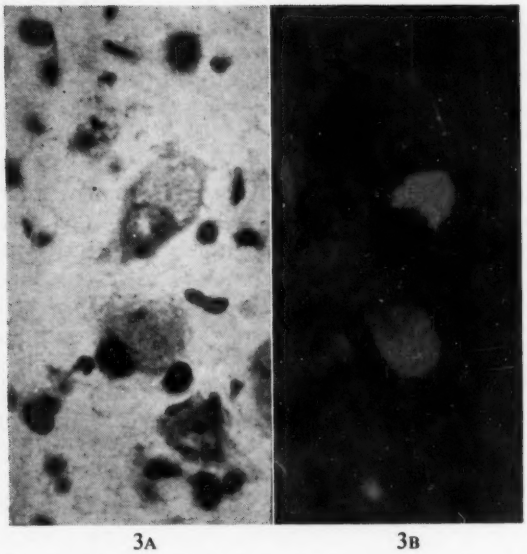


FIG. 2.—Longitudinal section of the adductor of the thigh showing fluorescent products lying inside the muscle fibres as well as in the endomysium. Unstained section. Reichert's "lux U.V." × 415.



3A 3B

FIG. 3.—Nerve cells from the intermedio-medial cell groups (autonomic zone) of the spinal cord. The cytoplasm is distended with lipoprotein substance; the nuclei show an eccentric displacement. (A) In daylight the lipoprotein is unstained. (B) In ultra-violet light the same lipoprotein is strongly fluorescent. Gallocyanin-chromalum and "lux U.V." × 625.

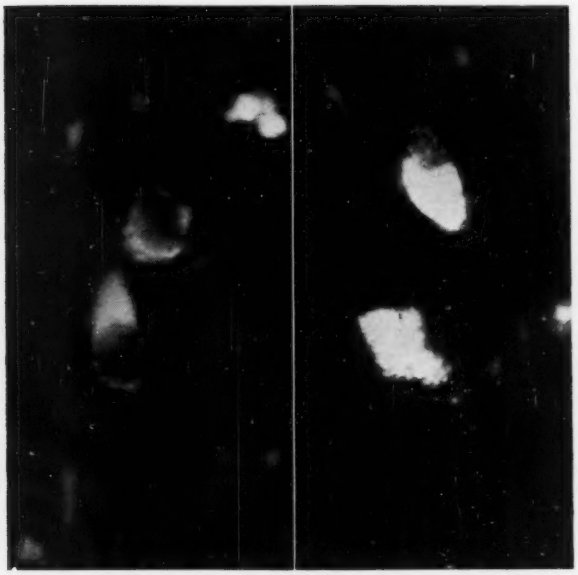
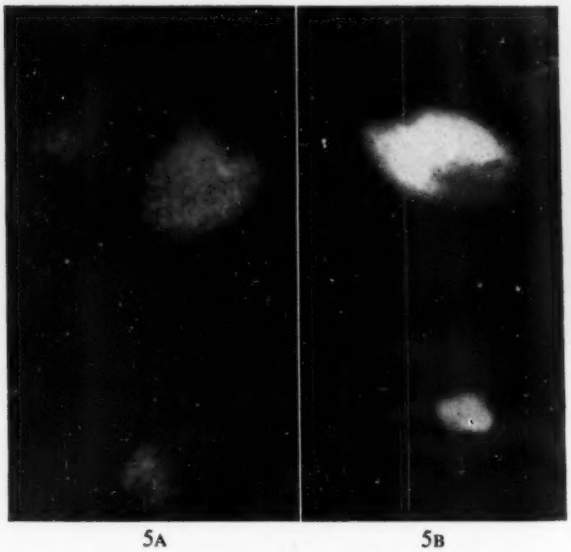


FIG. 4.—Nerve cells from the intermedio-lateral column of the spinal cord. The cytoplasm is filled with fluorescent products; the nuclei are more or less eccentric. Unstained section. "Lux U.V." × 625.

remnants of basophilic substance round the hyperchromatic, shrunken nucleus, or none at all. As far back as 1938 it was clearly pointed out by Einarson and Ringsted that this lipoid degeneration might completely dominate the stages of extreme chromophily and cell sclerosis. We have called this cell change "cellular lipodystrophy" (Einarson and Lorentzen, 1946; Einarson, 1949).

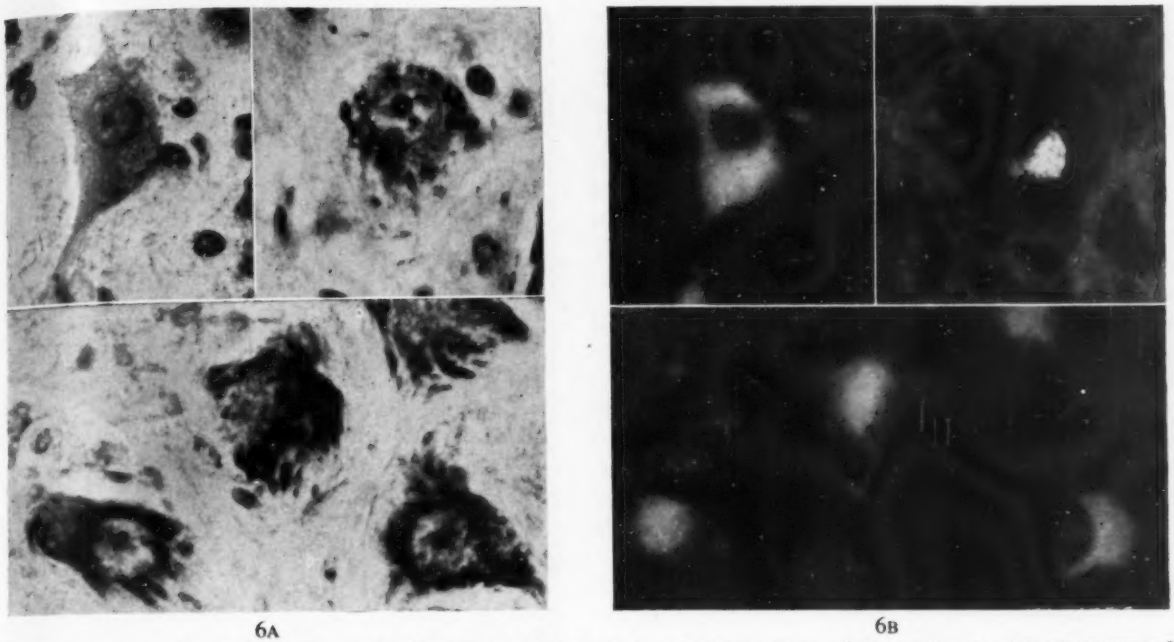
The acid-fast fluorescent products appear as diffuse or densely packed deposits of fine and coarse granules or globular particles in the cytoplasm of the nerve cells in or about astrocytes, oligodendrocytes, microglia and histiocytes, and in the walls of the blood vessels (Figs. 3–7, C–E). Unstained they show a greyish-yellow, sometimes rather dark colour. Besides their acid-fastness when stained by Ziehl-Neelsen's carbol-fuchsin, and their bright yellow primary fluorescence on ultra-violet irradiation, they are characterized by their relative insolubility in lipoid solvents, by staining reddish-orange with fat stains, by their affinity for basic aniline dyes, and by the fact that gallocyanin-chromalum leaves them completely unstained. These properties strongly suggest that we are dealing with a lipoprotein combination (ceroid) which does not contain nucleic acids (Einarson, 1949, 1952).

The irreparable lipodystrophic changes of the anterior horn cells will unavoidably put their stamp on the picture of the muscular atrophy: in other words, features of a late spinal atrophy are gradually superimposed on the early muscular dystrophy. Thus, the final picture of the muscular atrophy in the vitamin E-deficient adult rats reveals a combination of myogenic and neurogenic changes. The spinal-atrophic features manifest themselves by the occurrence of delimited patches of atrophic



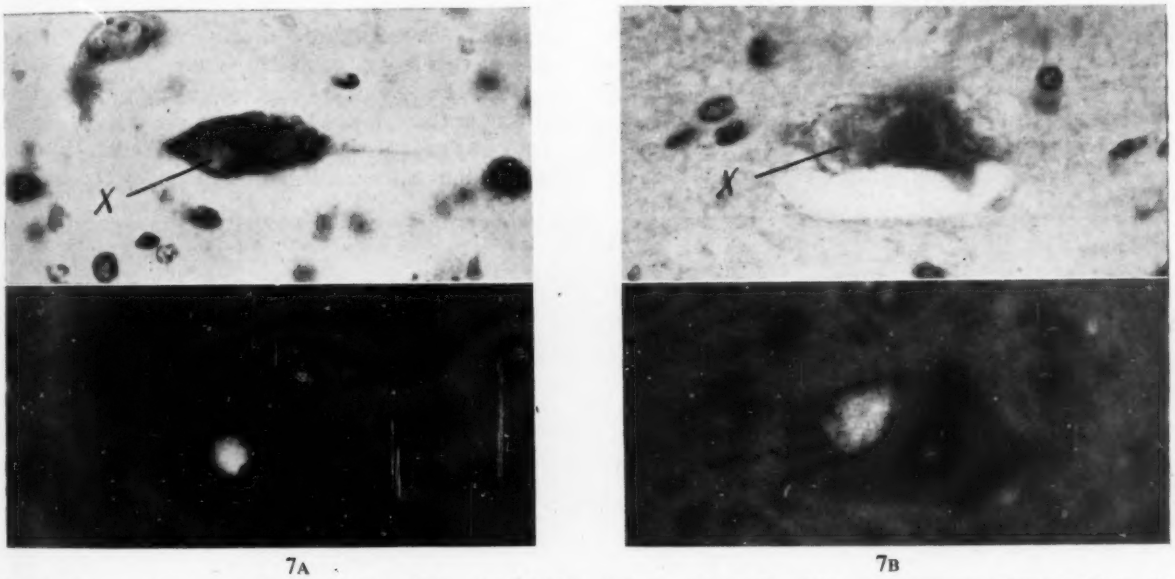
5A 5B

FIG. 5.—Anterior horn cells. Unstained section. "Lux U.V." × 625. (A) With coarsely globular, fluorescent particles in the cytoplasm. (B) With particles coalescing to a compact mass of fluorescent substance; the nucleus is shrunken and eccentric (cellular lipodystrophy).



6A 6B

FIG. 6.—Anterior horn cells with more or less lipoprotein substance in the cytoplasm. In some of the cells a considerable amount of stainable substance (ribonucleic acid) is still present. (A) In daylight the lipoprotein is unstained. (B) In ultra-violet light the lipoprotein is strongly fluorescent. Gallocyanin-chromalum and "lux U.V." × 625.



7A 7B

FIG. 7.—Two anterior horn cells in daylight and ultra-violet light respectively with small patches of fluorescent substance (X) in the cytoplasm. Gallocyanin-chromalum and "lux U.V." × 625.

(A) The cell is proceeding towards extreme chromophily; the nucleus is hyperchromatic. (B) The cell is proceeding towards irreparable atrophy with a loss of cytoplasmic basophily and hyperchromatosis of the nucleus.

muscle fibres. In the same field may be seen both the less atrophic and markedly atrophic fibres. In the final stage of the disease almost every muscle fibre has become atrophic. Further, the generally enormous increase of large hypolemmal nuclei, with well defined, markedly enlarged, and darkly staining nucleoli is a very characteristic sign that occurs specially in neurogenic atrophy. Moreover, the increase in sarcoplasm, the interruption of the muscle fibres by masses of sarcoplasm surrounding large nuclei with sharply defined, enlarged nucleoli, and numerous fluorescent inclusions, the preserva-

tion of the striation even in markedly atrophic muscle fibres, as well as the absence of hyaline or waxy degeneration, are features that speak decidedly for the interpretation of the late atrophy as being neurogenic. All these features constitute the spinal, atrophic phase of the process. The fact that it is possible to ascertain the appearance of the late neurogenic features is due only to the circumstance that they are not masked by the relatively mild development of the early myogenic changes.

Phase IV.—In phase IV there is swelling and fragmentation of myelin sheaths in the sciatic nerves, with deposits of fluorescent acid-fast lipoproteins in swollen Schwann cells, and particularly in histiocytes of the endoneurium (Fig. 8). The changes appear late and are comparatively mild, although numerous histiocytes may be seen to be filled with fluorescent particles; these products may also be seen accumulating round blood vessels of the endoneurium, as already shown by Einarson and Ringsted (1938).

Phase V.—In phase V there is a gradual development of severe nerve cell changes in the entire cerebrum. Their distribution is mostly diffuse and irregular. In the thalamus, hypothalamus, caudate and lenticular nuclei, as well as in the rhinencephalon and the non-olfactory cerebral cortex (neopallium) of the rats, numerous markedly changed nerve cells may be seen irregularly distributed among still normal or slightly changed cells. However, in the

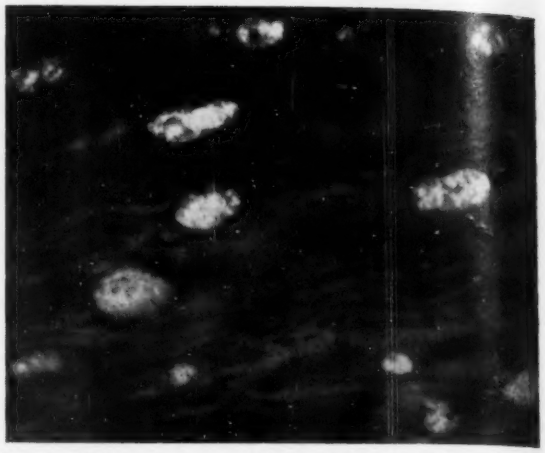


FIG. 8.—Sciatic nerve: many histiocytes of the endoneurium are filled with a strongly fluorescent substance. Unstained section. "Lux U.V." × 625.

rhinencephalon as well as in the layers of pyramidal cells of the neopallium long horizontal rows of distinctly affected cells may often be seen (Figs. 9 and 10).

Histologically the cell changes are the same as met with in the spinal cord and brain stem, and a further description is not necessary. I may just mention that the number of extremely chromophilic cells is decidedly increased as compared with the normal, and the fluorescent acid-fast products appear in the cytoplasm of the nerve cells in almost every region of the cerebrum. They are also to be found in or about the main types of glial cells, and

9A 9B

FIG. 9.—Neopallium. (A) Pyramidal cells showing more or less of strongly fluorescent substance in the cytoplasm. (B) Cortical blood vessel surrounded by fluorescent products. Unstained section. "Lux U.V." × 625.

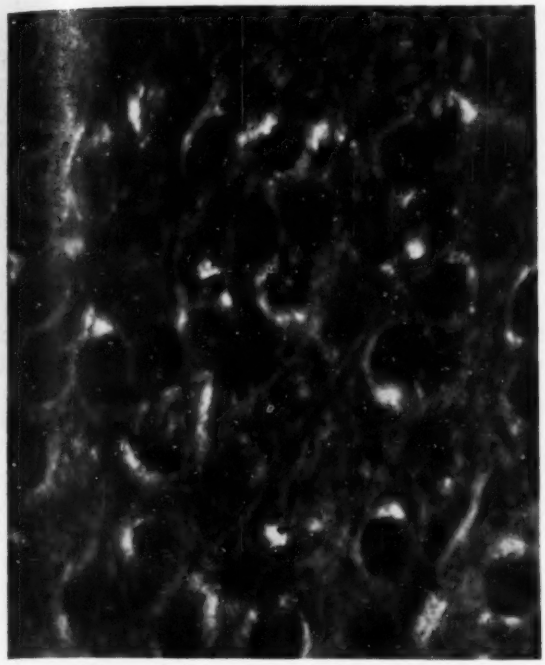
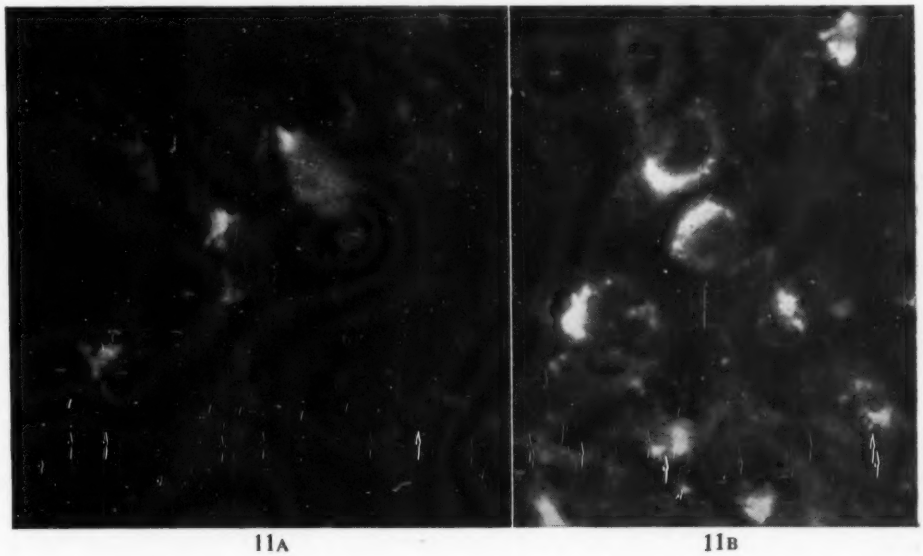


FIG. 10.—Rhinencephalon : nerve cells of the cortex showing fine granules of fluorescent substance diffusely distributed in the cytoplasm, especially round the nuclei. Small fluorescent particles are also lying in the glial cells. Unstained section. "Lux U.V." × 625.

in or round the walls of the blood vessels. Although numerous nerve cells containing considerable amounts of the fluorescent lipoproteins may be observed almost everywhere, the intracellular quantities of the deposits in question are on the whole somewhat less than in the spinal cord and brain stem. However, some nerve cells completely filled with these products may always be seen, and besides the more severely changed cells a great number contain a trace of the fluorescent acid-fast substance. Thus, " cellular lipodystrophy " is a widely distributed cell change in the cerebrum of the vitamin E-deficient adult rats.

Phase VI.—The late appearance of cell changes in the cerebellum is not distinctly visible until the final stage of the disease. Although the number of strongly chromophilic Purkinje cells seems to be increased compared with the normal, it is the occurrence of the lipoprotein inclusions that constitutes the most conspicuous feature of the changes. It is remarkable how the fluorescent acid-fast products finally appear in the cytoplasm of such decidedly " lipophobic " nerve cells as the Purkinje cells (Fig. 11). Also, they may be observed in the granular layer and in or about glial cells of the molecular layer, as well as round the blood vessels and in the central nuclei.

In the Purkinje cells the fluorescent acid-fast products are especially situated at the place of origin of the main apical dendrite from the cell body, often reaching down to the nuclear membrane and replacing more or less the basophilic nuclear cap. Sometimes they occupy a considerable portion of the cytoplasm of a Purkinje cell, even surrounding the whole nucleus. However, in each individual Purkinje cell we are mostly dealing with a comparatively small amount of fluorescent acid-fast substance, and, in consideration of the decidedly " lipophobic " character of this particular cell type, this is really to be expected. But, considering the fact that the most of the Purkinje cells show



11A 11B

FIG. 11.—Cerebellum. (A) Section perpendicular to the surface of a folium. Purkinje cells showing fluorescent substance especially situated at the place of origin of the main dendrite from the cell body. (B) Section parallel to the surface of a folium. Purkinje cells with considerable amounts of perinuclear fluorescent substance. Unstained sections. "Lux U.V." × 625.

these characteristic deposits, the phenomenon must be said to be extensively distributed in the cerebellar cortex.

Discussion

The results originally reported by Einarson and Ringsted (1938, 1939) were essentially confirmed by Monnier (1940, 1941, 1942) and by de Gutiérrez-Mahoney (1941), who found degeneration of the posterior fasciculi of the spinal cord, sclerosis, and irreparable atrophy of the nerve cells of the anterior horns and intermedio-lateral columns and slight demyelinization of the dorsal roots and peripheral nerves, but they did not mention the occurrence of any lipoid products in the nervous system of the rats. Monnier agrees with us that the muscular atrophy is a combination of myogenic and neurogenic changes.

Soon, however, the correctness of our results and concepts was seriously doubted by Mason (1942), and completely denied by Wolf and Pappenheimer (1942) and by Pappenheimer (1943). The last mentioned authors stated with certainty that, under the experimental conditions obtaining in their laboratory, lesions of the central nervous system did not occur in vitamin E-deficient rats at any age, and they actually regarded our findings as simply due to technical artefacts and misinterpretations. The results and conclusions of Wolf and Pappenheimer were supported by Harvey and Perryman (1944), and Lecoq and Isidor (1949), and recently the results and considerations of Einarson and Ringsted (1938) have been seriously criticized by Ruppel (1949) and Markees (1950), who apparently adhere to the interpretations and criticism of Wolf and Pappenheimer and Mason.

I shall not discuss these critical views in the present paper, but merely refer to my recent review of the concepts of the neuromuscular lesions in experimental vitamin-E deficiency (Einarson, 1952), in which I have clearly shown how unwarranted this criticism of Einarson and Ringsted's early work was and that the original interpretations of Einarson and Ringsted were essentially correct. Concerning the histological aspect of the effect of vitamin-E deficiency on the nervous system, the studies criticizing Einarson and Ringsted's results have actually failed, as the authors either have overlooked the occurrence of the neural lesions or they have misunderstood our interpretations. Moreover, it appears to me that some of the authors (e.g., Lecoq and Isidor) have not made any serious attempt to reproduce our experimental conditions. I also think that unfamiliarity with, and misunderstanding of, the gallocyanin-chromalum staining, which in an essential way deviates from the technique usually applied by the majority of investigators, invalidated much of the criticism.

Some essentials of our earlier observations have now been confirmed by the leading authors among those who formerly used to regard our findings as a mistake. Thus, Wolf and Pappenheimer (1945) and Pappenheimer and Victor (1946) have ascertained the regular occurrence of considerable amounts of acid-fast substance in the motor cells of the spinal cord and medulla oblongata in adult rats maintained for long periods on a vitamin-E deficient diet, and its absence in controls receiving protective doses of wheat germ oil or tocopherol. Indeed, the American authors did not find these products until they used carbol fuchsin for staining followed by decolorization in acid-alcohol. The fact that Wolf and Pappenheimer completely overlooked the occurrence of the lipoprotein inclusions in their first paper is partly due, I think, to their staining technique. They used toluidin blue and cresyl violet for the nerve cells, and these basic dyes stain the Nissl substance and the acid-fast products in approximately the same way, i.e., in a pure orthochromatic blue. Hence it may be very difficult or practically impossible to distinguish between the acid-fast products and true Nissl substance in such preparations. Gallocyanin-chromalum, on the other hand, leaves the acid-fast products completely unstained, and hence we could easily distinguish them from the selectively stained Nissl substance. We have repeatedly emphasized this very important fact, and the unstained, lipoprotein inclusions of the nerve cells were illustrated in our monograph. We also illustrated them in the sciatic nerves after staining with scarlet R. (Einarson and Ringsted, 1938). But all this was completely overlooked by Wolf and Pappenheimer (1942), as well as by all the other authors quoted above. Moreover, in their later papers Pappenheimer and his associates (1945, 1946) have completely omitted to consider our earlier findings.

I wish to emphasize that the fluorescent acid-fast products are much more widely distributed in the nervous system of the vitamin E-deficient rats than maintained by Wolf and Pappenheimer and Pappenheimer and Victor, who found them only in the motor cells of the spinal cord and medulla oblongata. In this paper I have demonstrated that the products in question are distributed practically all over the nervous system (Phases III–VI).

Furthermore, the degeneration of the posterior spinal fasciculi and dorsal roots (phase I), as originally reported by Einarson and Ringsted (1938), has been fully confirmed by Luttrell and Mason (1949) and by Malamud, Nelson, and

Evans (1949). Apart from the fact that the authors quoted do not have a word to say about the occurrence of any fluorescent acid-fast products in the posterior fasciculi, I have nothing to remark ; as for the rest, their findings are in complete agreement with our earlier observations. But the vast distribution of the fluorescent acid-fast products in nerve cells, glial cells, histiocytes, and the walls of the blood vessels practically all over the nervous system (phase III–VI) has apparently escaped their attention, although Luttrell and Mason have used Kinyoun's carbol fuchsin staining, and Malamud and others mention a slight increase in fat content of the anterior horn cells. These authors maintain, just as Pappenheimer and his associates (1945, 1946) do, that there are no changes whatever to be found in the brain in experimental vitamin-E deficiency.

A very striking characteristic of the neural changes produced by experimental vitamin-E deficiency is their early irreversibility. Serious clinical disturbances develop at a time at which structural changes are barely or not at all detectable by our present technique, and yet the disease progresses in spite of the therapeutic administration of vitamin E. In my opinion, this demonstrates that the changes must start at a submicroscopic, biochemical level, and their structural manifestation at the microscopic level is essentially a function of the time factor. Whether the electron-microscope might reveal some subtle, initial changes I am not able to say.

This early irreversibility of the experimental changes must be borne in mind as regards the clinical treatment of patients with vitamin E. Whether a deficiency or a defective utilization of vitamin E (dysvitaminosis) is a concurrent factor in the development of neural or neuromuscular disorders in man is still questionable. But even if this actually were so we could not expect much from vitamin-E treatment alone, since the lesions produced in adult rats, by deprivation of the vitamin itself, are practically irreversible and uninfluenced by the therapeutic administration of vitamin E. This was clearly emphasized by Einarson and Ringsted (1938), but it has apparently been overlooked by the majority of those clinicians who have been engaged in treating patients suffering from neuromuscular disorders with vitamin E. The largely negative or equivocal results from the clinical treatment with vitamin E are completely in accordance with the therapeutic experiments on rats, in which the disease is incurable by vitamin E.

Furthermore, I wish, in particular, to emphasize the following points :—(1) The almost ubiquitous occurrence of fluorescent acid-fast substance (lipoprotein) in the nervous system of adult rats that have long been kept on a vitamin-E deficient diet, and its regular absence in controls receiving protective doses of vitamin E. (2) In the cytoplasm of the nerve cells the amount of fluorescent acid-fast substance is inversely proportional to that of the nucleic acid ; in other words as the fluorescent acid-fast substance increases, the ribonucleic acid of the cytoplasm gradually disappears, a cell change accompanied by a more or less eccentric displacement, hyperchromatosis, and shrinkage of the nucleus (" cellular lipodystrophy "). (3) The early appearance and marked intensity of the cell changes in the autonomic centres of the spinal cord and brain stem : thus, in the entire intermediolateral cell columns, as well as in the medial cell groups of the intermediary zones of the spinal cord, the cells appear completely filled with fluorescent acid-fast substance, already at the end of the second or the beginning of the third clinical stages.

The last point (3) might be of great importance in the whole syndrome of the vitamin-E deficient rats, a possibility duly considered by Einarson and Ringsted (1938), Evans (1940), and Einarson (1941), who supposed that a primary injury to the autonomic nervous system might be involved in this particular deficiency. It might be surmised that a disturbance of the balance of autonomic regulations concerned with the vasomotor and metabolic controls of the tissues took place. Actually, the work of Martin (1946) on the action of prostigmine in the nutritional muscular dystrophy of vitamin-E deficiency is in support of this hypothesis. Also, I refer to my recent considerations on this particular point (Einarson 1949, 1952).

In conclusion, I think it is justifiable to state that vitamin E is essential to the normal health and the structural and functional integrity of the nervous system in the rat. This cannot be a surprise since vitamin E is involved in certain fundamental biological oxidations, and possibly in some phosphorylations as well, although its ultimate physiological action is still obscure. The fact that experimental vitamin-E deficiency produces conspicuous microscopic lesions in many organs and tissues clearly shows that its function in tissue metabolism must be of an almost universal importance in the organism. The idea that the nervous system should escape the injurious effect of experimental vitamin-E deficiency is, in my opinion, incompatible with our present knowledge of the physiology and biochemistry of vitamin E (Einarson, 1952).

Finally the fluorescent acid-fast products des-

cribed in this paper are not to be regarded as something specific for vitamin-E deficiency. Although the products deviate from the usual soluble lipochrome, which stains a brilliant red with scarlet R, they may be observed in human necropsy material, both in the nervous system and elsewhere, more or less mixed with the usual lipochrome substance. Possibly, the commonly occurring lipochrome is a mixture of substances, some of which are fluorescent and acid-fast and relatively insoluble in the usual fat solvents. But, in order to produce such fluorescent and acid-fast products in large amounts in the tissues of animals, experimental chronic vitamin-E deficiency is a most effective and important procedure.

Summary

Neuromuscular lesions, in particular the regular occurrence of deposits of fluorescent, acid-fast products in the nervous system and skeletal muscles of adult rats that have long been kept on a vitamin-E deficient diet, are reported. The findings generally confirm the earlier observation and description by Einarson and Ringsted (1938) of these neuromuscular lesions, and in particular of lipoid products in the nervous system of adult rats in chronic vitamin-E deficiency. Furthermore, it is demonstrated that the nerve cell changes and the acid-fast deposits are far more widely distributed in the nervous system than was previously thought.

A brief account is given of the clinical symptoms displayed by rats, and some remarks on technique.

The histological examination clearly shows that the disease is due to a combination of neurogenic and myogenic lesions as originally maintained by Einarson and Ringsted (1938, 1939). The lesions consist of degeneration of the dorsal roots and posterior fasciculi of the spinal cord, myogenic changes of the skeletal muscles followed by pronounced changes of the visceral and somatic motor and sensory cells of the spinal cord and brain stem, as well as of the cells of the spinal and cranial ganglia, and gradually features of neurogenic muscular atrophy are superimposed on the earlier myogenic changes. Somewhat later there appear mild changes in the sciatic nerves and marked diffusely distributed cell changes in the central nuclei of the brain and the entire cerebral cortex, followed by mild cell changes in the cerebellum.

Everywhere the changes are highly characteristic of the lipoid products. Besides staining reddish-orange with fat stains they are characterized by their relative insolubility in lipoid solvents, their affinity for basic aniline dyes (orthochromatic staining), their acid-fastness when stained by Ziehl-Neelsen's carbol fuchsin, their bright, yellow, primary fluorescence on ultra-violet irradiation, and by the fact that they are left completely unstained by gallocyanin-chromalum, a stoicheiometrical staining reaction for nucleic acids. These properties strongly suggest that we are dealing with a lipoprotein combination (ceroid) which does not contain nucleic acids.

The fluorescent acid-fast products appear as fine, rounded granules or coarsely globular particles, sometimes coalescing to compact masses. They lie in the cytoplasm of the nerve cells, in or about glial cells and histiocytes, and in the walls of the blood vessels, and they occur almost all over the nervous system. In the muscles they lie both inside and outside the muscle fibres. They are regularly absent in controls receiving protective doses of vitamin E.

In the nerve cells the progressive increase of the fluorescent acid-fast substance invariably involves a corresponding decrease in the ribonucleic acid of the cytoplasm until it completely disappears, a cell change accompanied by more or less eccentric displacement, hyperchromatosis, and shrinkage of the nucleus ("cellular lipodystrophy". The early appearance and marked intensity of this cell change in the autonomic centres of the spinal cord and brain stem is particularly emphasized.

The changes must start at a submicroscopic, biochemical level, and their early irreversibility is pointed out.

Fluorescent, acid-fast products comparable with those described in rats may be observed in human necropsy material, more or less mixed with the commonly occurring lipochrome.

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AN EXTREMELY RARE RECESSIVE HEREDITARY SYNDROME INCLUDING CEREBELLAR ATAXIA, OLIGOPHRENIA, CATARACT, AND OTHER FEATURES

BY

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Under the title of " Nouvelle maladie familiale caractérisée par une cataracte congénitale et un arrêt du developpement somato-neuropsychique " a paper was written by Marinesco, Draganesco, and Vasiliu in 1931 describing four siblings clearly suffering from the same disorder, a syndrome which had not been previously described. Sjögren (1950) reported 14 similar patients, discovered after painstaking search throughout Sweden, and he believed this to be only the second time the syndrome had been observed ; he, however, was able to prove beyond doubt that this is a hereditary disorder, due to a single autosomal recessive gene and frequently resulting from consanguineous marriage.

In 1933 one of us was asked by Professor C. W. Vining to examine two children then under his care. They were first cousins apparently suffering from an identical and congenital syndrome. There was a remarkable history of consanguinity in the family but at that time it was not clear whether the disorder, in all its aspects, was stationary, and it was difficult to assess the intellectual level of the patients. They were not seen again until one of them was referred to us in 1951. It was then possible to make a more accurate clinical assessment, and both were admitted to the Neurological Department of the General Infirmary at Leeds for more detailed investigation in September, 1952.

Case Reports

Case 1.—A boy was born on December 24, 1925. He was a full term child weighing 8½ lb. (3·8 kg.) and the fifth of seven siblings. He was never jaundiced. It was noted at 3 weeks that he could not suck normally, he was late in sitting up, but he learned to crawl quickly. Defective speech appeared at about 9 months and was slow, but he always tended to be talkative. He was quick tempered and liable to cry but was said to play normally ; he never had convulsions and was clean in his habits at 1 year. When examined by one of us at the age of 6, he had a slow and grossly dysarthric, almost unintelligible, speech. His mouth was always open, with constant salivation. He was unable to walk, but could stand alone against a wall (Fig. 1) and attempted to walk with support. All the limbs were grossly ataxic, but there was no obvious dystonia or reflex change and the plantar responses were flexor. At this time the mother's general impression was that he was improving.

He was more fully investigated in September, 1952, when his height was 5 ft. 6 in. (165 cm.) and weight 7 st. 8 lb. (48 kg.). His general health had always been excellent ; he had whooping cough at 5 and scarlet fever at 7. He started to shave at 16, and shaved daily ; hair distribution was normal. During examination he was very cooperative, asking many questions particularly with regard to possible treatment. He was fond of going out in a wheel-chair and of listening to the wireless. He was able to feed himself with a spoon and to dress himself, apart from fastening buttons.

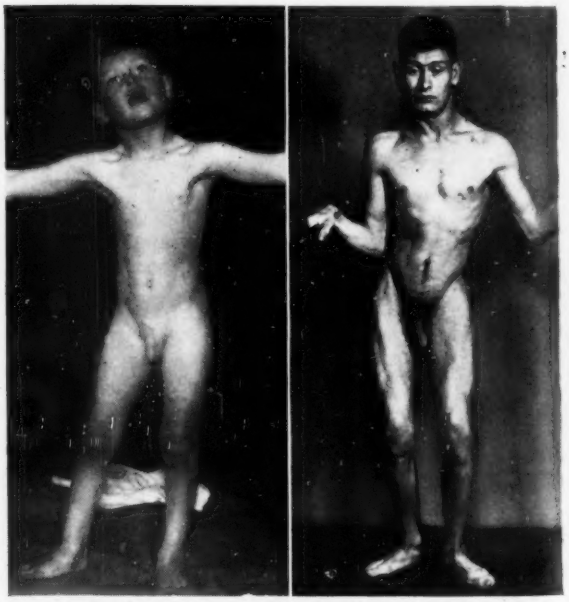

FIG. 1.—On the left Case 1 aged 6, and on the right the same patient aged 27.

His usual mood was euphoric, but he was easily upset. Speech was slow and so slurred as to be almost unintelligible. The fundi could not be seen because of bilateral cataract; he was able to count fingers at about 3 ft. There was a continuous coarse nystagmus in all directions, with a rotatory element, eye movements being full apart from an inability to converge. The pupils were large but reacted normally to light. Although there was no obvious facial weakness he had difficulty in showing his teeth and was unable to whistle. He was right-handed. His grip was good and equal on both sides, indeed there was no obvious muscular weakness but a striking feature was the widespread firmness of the muscles, visible in Fig. 1. Ordinary methods of testing demonstrated no dystonia in the arms but the outstretched hands were held in a hypotonic attitude. Alternating movements at both wrists were very defective and there was gross ataxia of a cerebellar type in the finger-nose test. There was some limitation of extension at the knee joints, with slight *genu valgum* and some increase of tone in the legs; there was gross ataxia of a cerebellar type in the heel-knee test. All the tendon reflexes were extremely brisk, the abdominal reflexes present, and the plantar responses equivocal. He was unable to walk alone and the gait was slow and very ataxic. There was no sensory loss of any kind. There was a constant tachycardia (about 90 per min.), blood pressure 160/100 mm. Hg, slight lower dorsal scoliosis, and a deformity of the right fourth and fifth toes.

Electro-encephalography (Dr. M. J. Parsonage).—The record contained a considerable amount of artefact mainly due to eye movement. Basically it was of low voltage but showed no abnormal activity at any stage.

Psychometry (Mr. D. R. Martin).—Throughout the examination the patient was friendly and tried hard, but visual and motor disabilities made the testing difficult. On the Kent Oral Emergency Scale (scale D) he scored 13. His mental age was 8 years (I.Q. about 55). On the Wechsler-Bellevue Intelligence Scale Form I (verbal scale only) the I.Q. was 67. There was a general impression that with special training the patient would improve in ability although functioning at the feeble-minded level.

Ophthalmic Examination (Mr. J. Foster).—There was a bilateral cataract composed of minute dots, occupying the adult as well as the embryonic nucleus, thinner at the centre than at the edges and showing well marked water clefts. The fundi could not be clearly seen.

Electrocardiography (Dr. I. Macpherson).—The record showed low T waves and slight depression of the S-T segments in leads 2, 3, and V6, suggesting early left ventricular preponderance, in keeping with slight left ventricular hypertrophy.

Radioscopy showed no abnormality of the skull.

Case 2.—A girl was born on January 16, 1928, and was the seventh of nine siblings. She was a full-time child, delivered normally and weighing 8 lb. (3·6 kg.); she was never jaundiced. The parents did not realize there was any abnormality until it was noticed that she would not sit up or try to crawl at 9 months. She was clean in her habits at 1 year, but attempted to talk only at 3, and about this time she had a single convulsion. At 5 years she was unable to walk unaided, the gait being very ataxic. It was thought that distant vision was defective and there was continuous nystagmus with a rotatory element; speech was very limited and grossly dysarthric. There were no reflex changes, the plantar responses being flexor. She was a shy child, easily annoyed and often crying. The mouth was usually open (Fig. 2).

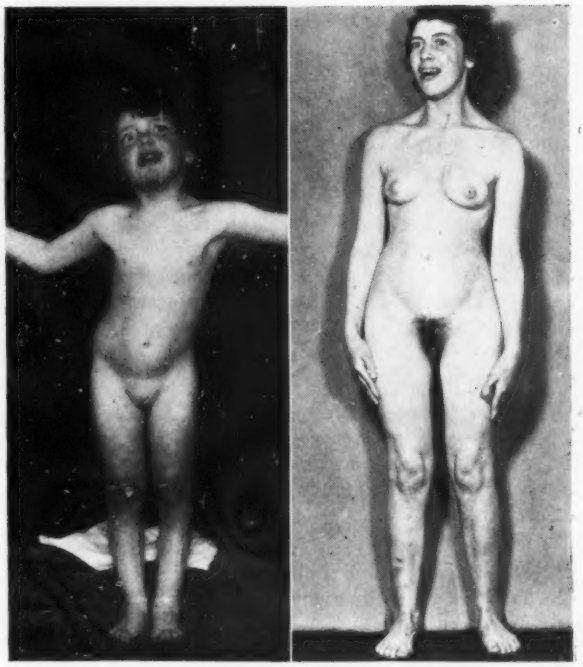

FIG. 2.—Case 2 at 5 years and the same patient aged 24.

In September, 1952, she weighed 7 st. 1 lb. (44·5 kg.) and was 5 ft. (150 cm.) tall. She was almost unable to close the lips and had a constant and fatuous grin (Fig. 2). She was euphoric, very easily amused, cooperative, and had an excellent memory; she remembered Professor Vining, whom she had not seen for 20 years, though he had forgotten her. Speech was slow, very slurred, and similar to that of her first cousin (case 1) but she was much more intelligible. She was able to dress and feed herself. She had enjoyed excellent health, having only suffered from measles, whooping-cough, and chickenpox. Menstruation started at 14 and was regular; hair distribution was normal and mammary development full. The right fundus could not be seen because of cataract; there had been a left capsulotomy on August 7, 1952, and she could count fingers at 2 ft. The pupils were large and equal and reacted normally to light, but she was unable to converge and there was continuous gross nystagmus in all directions. She was right-handed. There was no weakness of the arms but the outstretched hands were held in a hypotonic posture. Alternating movements at the wrists were very defective

and there was gross ataxia of the cerebellar type in the finger-nose test. There was no weakness of the legs, but tone was slightly increased and there was gross cerebellar ataxia in the heel-knee test. All the tendon jerks were very brisk, the abdominal reflexes present and the plantar responses undoubtedly extensor. The muscles in this patient did not show the same firmness as in case 1. She was able to stand unsupported and could jump and hop on either foot rather clumsily. She walked on a broad base and was very ataxic, with a tendency to fall unless supported. There was no sensory abnormality. There was constant tachycardia (about 96 per min.); blood pressure was 150/100 mm. Hg. There was a dorso-lumbar scoliosis and deformity of both fifth fingers and toes.

Electro-encephalography (Dr. M. J. Parsonage).—There was no abnormality during 15 minutes' continuous recording, and basically the record was of the low-voltage-high-frequency type containing no activity of alpha frequency.

Psychometry (Mr. D. R. Martin).—The patient was cheerful, friendly, and trying hard throughout the tests. On the Kent Oral Emergency Scale (scale D) she scored 18. Her mental age was 10 years (I.Q. about 65). On the Wechsler-Bellevue Intelligence Scale Form 1 (verbal scale only) her I.Q. was 61. The intellectual efficiency was at the feeble-minded level, though she gave a general impression of being more intelligent than this, and it was felt that she might improve with special education.

Air-encephalography.—Air, 40 ml., was introduced intrathecally and revealed no abnormality of the ventricular system. The cerebrospinal fluid was normal in all respects and there was no radiological abnormality of the skull.

Ophthalmic Examination (Mr. J. Foster).—The patient was first examined in 1951, when she was found to have a fine punctate bilateral cataract consisting of a multitude of tiny dots, of the type which used to be regarded as associated with glandular dyscrasia. Capsulotomy was carried out on August 7, 1952; it was then found that the optic disc was pale but it was impossible to see details of the fundus clearly because of nystagmus and it was thought that the latter was largely responsible for the poor vision.

Electrocardiography (Dr. I. Macpherson).—There were small Q.R.S. complexes in lead 1, almost certainly due to a vertical heart position, but the record contained no other abnormality.

Pedigree of Cases 1 and 2

Fig. 3 shows the very remarkable family history of the two patients described (V, 7 and 14). It will be seen that they are the descendants of the same pair of great-great-grandparents. The pedigree shows that consanguineous marriages occurred four times in two generations (III and IV), that the mothers (IV, 1 and 2) of the two patients were sisters and that each of the four parents (III, 1, IV, 1, 2, and 6) was related to the other three. This pedigree has been constructed through the help of the three sisters (IV, 1, 2, and 4) and

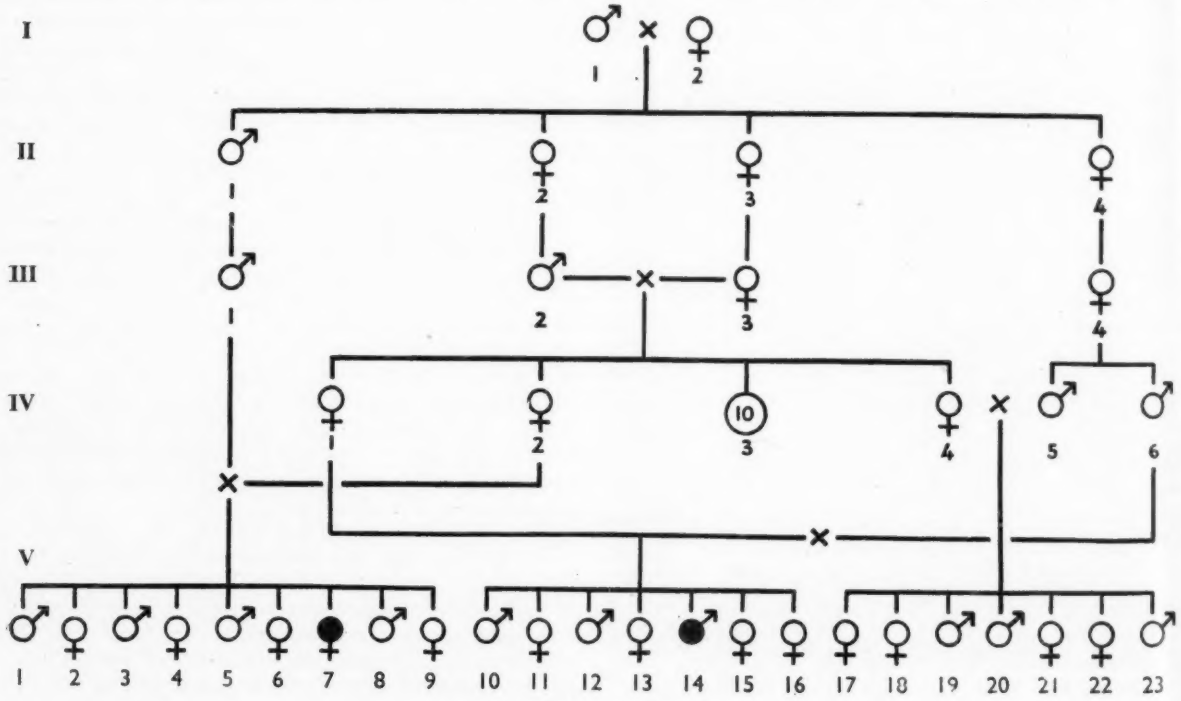

FIG. 3.—Pedigree of cases 1 and 2.

their husbands. One sister (IV, 4) married a second cousin (IV, 5); there are seven children (V, 17–23) who are all alive and well. The circle (IV, 3) represents 10 siblings all said to be normal; as far as we know there were no consanguineous marriages, but most are married and have normal children. The sister (IV, 1) also married a second cousin (IV, 6) who is the brother of the man (IV, 5) who married her sister (IV, 4). There were seven children (V, 10–16) of this marriage; the fifth is case 1 and the second and sixth (females, V, 11 and 15) are alive and well. The first (male, V, 10) died in convulsions after a few days; he weighed 14 lb. (6·3 kg.) and probably had a birth injury. The third (male, V, 12) died at 7 months in convulsions, the fourth (female, V, 13) died at 3 months also in convulsions, and the seventh (female, V, 16) died at 2 weeks of an umbilical haemorrhage. The sister (IV, 2) married a man (III, 1) considerably older than herself who was a first cousin of both her parents (III, 2 and 3), who were themselves first cousins; they had nine children (V, 1–9), of which case 2 is the seventh, all the others being alive and well. Further details of generations I to IV are not known but the persons interviewed are satisfied that there are no others in the family similarly affected, nor are they aware of any examples of cataract or of mental deficiency. It is, of course, impossible to make any pronouncement about the four siblings in generation V who died in infancy, but of the remaining 12 in generation V, 1–16, only two are affected. There are no affected persons in the sibship V, 17–23 but here the recessive factor may not have been carried by both parents. The incidence of consanguinity in this family is particularly striking since they are not found in an isolated village community but all lived in sizeable (and different) industrial towns in the West Riding of Yorkshire, to which generation III appears to have moved from Staffordshire.

Comments on Cases 1 and 2

It will be generally accepted that the two patients described are suffering from the same disorder. Perhaps the most striking feature is the congenital and widespread ataxia, of cerebellar type, associated with gross dysarthria and nystagmus. We are satisfied, despite the suggestions of the parents, that this aspect of the syndrome is stationary, and the history suggests very strongly that the cerebellar defect is of developmental origin. There is no doubt that both patients are mentally backward. A precise assessment is impossible because of the absence of education together with the visual, speech, and motor defects, but the general impression even in childhood has been that intelligence is not so inferior as a superficial examination would suggest. Both suffer from cataract of an unusual and similar type and there is no doubt that this has been progressive. It was not detected by one of us on routine examination in childhood, though it was thought that the vision in case 2 was not normal at 5 years and she became blind at an earlier age than her cousin (case 1). It would seem likely that he will become blind unless or until he is suitable for capsulotomy. We are satisfied that there is no defect of sensation, but there is evidence of pyramidal tract involvement in both patients, as shown by very brisk tendon jerks, increase of tone in the legs, and undoubted extensor plantar responses in case 2. Both are undersized and show minor skeletal deformities, including scoliosis, *genu valgum*, limitation of extension of the knee joints, and anomalies in the fingers and toes, with electroencephalograms which are normal, persistent tachycardia, and moderate hypertension. Both enjoy good health and in neither is there evidence of endocrine dysfunction. There are only small differences between the two and these are mostly of degree.

Analysis of Previous Reports

Marinesco and others (1931) realized that four siblings were suffering from the same disorder, which had probably not been described before, but unfortunately their paper contained serious errors. They described two normal (married) Roumanian peasants. There had been 10 pregnancies, including one stillborn child and three others dying in infancy. Of the remaining six, two were examined and said to be normal, and case histories of the other four (one male, three females) were recorded, but there was an unfortunate reference later in the paper to *five* similarly affected persons (one male, four females); who the fifth affected female was remains a mystery. To add to the confusion, Sjögren (1950) in referring to the Roumanian paper stated that " the disease occurred in five sibs (four boys and one girl) ". At this late stage it would seem reasonably certain that the Roumanian sibship consisted of a stillbirth, three children who died in infancy, two unaffected males, and four affected siblings (one male, three females), or that of six siblings who survived beyond the first year, four were affected with the same disorder. In this family all four affected persons were noticed to have failing vision in the third year, in each proceeding to blindness from cataract within a year or two. In the eldest affected person (female, aged 18) the cataract was noted to be densest in the middle, with

a peripheral clear ring. In none was the cataract treated. All four were considerably undersized, as is well shown in photographs. They showed notable clumsiness of all four limbs, with signs characteristic of a cerebellar defect and with muscular hypotonia. At the time of examination (aged 18, 17, 8, and 4) all showed brisk tendon and abdominal reflexes, with flexor plantar responses, and it was thought that the cerebellar defect was complicated by a pyramidal disturbance. This family had been under observation for several years, and there was a suggestion that in two patients the neurological syndrome might have been progressive. All four showed a well marked mental defect. A girl of 18 did not know her right hand from her left, and the mental state in a boy of 17 was said to be even worse, but the mentality of the other two was not described in detail. Three of the four were said to show old rachitic deformities and *x*-ray changes were noted in the terminal phalanges of two. A biopsy was carried out on the right frontal cortex in one patient (female, aged 8), and the histological changes were described in considerable detail, showing atrophy of ganglion cells and a paucity of nerve fibres. For some reason, which is not clear, serum calcium estimations were carried out on six members of the family, and in one affected child the level was certainly low (6·9 mg.%) but it was also low (7·7 mg.%) in the normal father (incorrectly referred to by Richards (1950) as the mother) and in one of the normal brothers (6·7 mg.%) and was slightly low in another affected sibling (8·5 mg.%). It seems highly probable that these figures are either inaccurate or irrelevant. Although the authors recognized that four members of a family were suffering from a disorder which they believed to be unique, it apparently did not occur to them that it might have resulted from a hereditary factor, and they were fairly convinced that the syndrome resulted from an endocrine dyscrasia, drawing some parallel with cretinism. They were also somewhat minded to invoke vitamin deficiency, though admitted that it was difficult in that case to explain away the normal members of the family. Whether or not the parents were blood relations will presumably never be known.

Sjögren (1950), after a preliminary report in 1947, agreed that the Roumanian family had been unique, but then described a group of similar patients. He had found 14 affected persons in three families. Family A consisted of five generations, and in the third generation there were two consanguineous marriages (A2 and A3). There were 10 children of the marriage A2 (three males, seven females), of whom one male and one female were affected, and nine children of the marriage A3 (two males, seven females), of whom two females were affected. The parents of family A1 were a normal male from A2 and a normal female from A3 ; their marriage resulted in nine children (three males, six females) of whom three females were affected. In the three sibships, A1, A2, and A3, therefore, there were seven affected persons (one male, six females) all the results of consanguineous marriages, all the parents of affected persons being first cousins. Sjögren's second pedigree (family B) also refers to five generations. In the fourth there is a sibship of five (three males, two females) with one affected male, and in the fifth generation there is a sibship of 10 (six males, four females) in which three males and one female were affected. Again, all the affected persons resulted from marriage between first cousins. In family C there were two affected siblings (one male, one female). The parents were said to be normal and there was no evidence of consanguinity. No further details were given.

Unfortunately only four of the 14 had been personally examined (one in each of families A and B and the two in family C) though there seems to be little doubt that all 14 suffered from the same disorder. Of the four personally examined two were males and two females. The first (female, aged 43) had been under observation for almost 20 years. She showed a mental defect which was not progressive, an ataxic gait which was slowly progressive, blindness from cataract when first seen, widespread weakness of the limbs with moderate hypotonia and marked cerebellar ataxia, dysarthria, and nystagmus. The tendon reflexes were brisk and the plantar responses extensor. She was undersized and showed scoliosis and bilateral talipes. The second (male, aged 38) had also been under observation for many years. He was known to have a severe mental defect from infancy, with congenital cataract progressing to blindness, and there was widespread weakness of the limbs, with cerebellar ataxia, nystagmus, and dysarthria. The tendon reflexes were brisk in 1931 and diminished in 1948 ; the abdominal reflexes were normal and the plantar responses were equivocal in 1931 and extensor in 1948. He was undersized and showed a kyphoscoliosis and talipes, with vasomotor changes in the feet. The third (female, aged 25) had shown a severe mental defect from birth, lifelong disturbance of gait, and bilateral cataract first diagnosed at the age of 6. She was undersized and showed widespread weakness of the limbs with cerebellar ataxia, dysarthria, and nystagmus. The tendon reflexes were normal and the plantar responses

extensor. She had a pronounced kyphosis and talipes. The fourth (male, aged 22) was mentally defective from birth, with bilateral cataract first diagnosed at the age of 3. He also had widespread cerebellar ataxia, dysarthria, and nystagmus. The plantar responses were extensor and the tendon reflexes brisk. He was undersized and showed kyphosis and talipes.

Richards (1950) was familiar with the Roumanian paper and with the preliminary report of Sjögren (1947). He described two patients with cataract, mental deficiency, and a neurological disorder, being the only two so affected in a population of 2,000 mentally defective persons. The first case was a female, aged 11 years who was illegitimate and for whom no family history was available, though there was a normal younger sibling. This child had been under observation for nearly eight years. A central lens opacity had been detected at the age of 6 and the cataract was subsequently progressive ; there was a strabismus but (presumably) no nystagmus. At all stages speech was said to be normal. The I.Q. (Terman-Merrill) was 68. The neurological picture is rather confused ; at 3½ years the child was said to have total areflexia, but at 10 only the triceps jerks were absent. The plantar responses were extensor. She was said to have good muscular power, slight intention tremor, but a very unsteady gait. The second case was a male, first seen at 35 and finally described at 47. He was not the result of a consanguineous marriage and there was a twin of the same sex who died at 7 months. He was said to have learned to read quite well but no attempt had been made to assess the level of intelligence in early life ; later, as an adult, his mental age was assessed at 10 years. He was under-height, almost blind from cataract and choroiditis, with total areflexia and extensor plantar responses, and there was a slight intention tremor. Although it is admitted that these two patients showed cataract, a mental defect, and a neurological syndrome, it is felt that there are so many differences between these patients and those described by Marinesco and others (1931), Sjögren (1950), and ourselves that it is possible these are examples of a different syndrome and, indeed, there is nothing to show that either was suffering from a genetic abnormality. We therefore do not propose to discuss these two patients further.

Discussion

To Marinesco and others (1931) must be given the credit for recognizing a new syndrome and for providing the only histological studies at present available. They observed that the syndrome consisted of cataract, oligophrenia, and a neurological picture including both cerebellar and pyramidal features. They also noticed that the affected persons were undersized. Though commenting on skeletal anomalies, they attributed these, probably incorrectly, to rickets, and their views as to aetiology in general are quite unacceptable.

To Sjögren (1950) is to be given the credit for recognizing this syndrome for the second time and for realizing for the first time that it resulted from a single autosomal recessive gene. It would, however, be unfortunate if Sjögren's name were applied to this syndrome as an eponym since an entirely different disorder is already accepted in current literature under this eponymous title (Sjögren, 1933).

We have been unable to trace any other examples of this syndrome in the world's medical writings, nor are Professor Arnold Sorsby (1952) and Dr. Julia Bell (1952) familiar with any other records. Having discarded the cases reported by Richards (1950) we are reduced to the discussion of 20 persons, four from Roumania, 14 from Sweden, and two of our own. This discussion must be divided into two parts because important details of the pedigree are lacking in the Roumanian family and only four of the 14 Swedish examples had been examined, so that the genetics of the syndrome can only be related to 16 of the patients and the clinical syndrome to 10.

Sjögren pointed out that five out of six of his sibships containing affected persons were the result of first cousin marriages, or 83 ± 17%. One of our own sibships (V, 1–9) is the result of a marriage which can be considered as equivalent to that of first cousins ; in the second (V, 10–16) the relationship is more distant. Hence, adding our figures to those of Sjögren, six out of eight of the sibships have resulted from first cousin marriages, or 75 ± 16%, and seven out of eight have resulted from consanguineous marriages, or 88 ± 14%.

It is well known that the rarer a recessive gene the more frequently is there a history of consanguinity in the parents of affected persons, and on this basis it would seem that the syndrome under discussion results from one of the rarest known recessive genes in man.

From the available clinical evidence the total syndrome appears to be as follows. Of the 20 affected persons eight were males and 12 were females. The first recognizable features have usually been the cerebellar ataxia, though cataract was detected in some at an early age. The mental defect has probably never been of the most serious order and it is not surprising that it was often not

recognized until adult life, though Marinesco and others (1931) suggested that in their patients the defect was detected at an early age. Still later has it become apparent that these persons are always undersized. Details relating to the cataract are not always available though it would seem clear that in some the cataract is evident in early childhood, that it probably always progresses to complete blindness, but the age at which blindness appears varies considerably from early childhood to young adult life. The skeletal anomalies are usually of a minor kind but include kyphoscoliosis, *genu valgum*, deformities of the digits, and talipes. There is no suggestion that the oligophrenia is progressive, and only scanty evidence that the degree of ataxia increases. There is clinical evidence in several recorded patients of involvement of the pyramidal system and, although the total disability may not have increased, the plantar responses in some patients have become extensor with the passage of time. There has been no previous reference to the cardiovascular system, but it is probably significant that both our patients were suffering from vascular hypertension in young adult life.

Genetic disorders in man are known to affect particularly the central nervous system, the eye, and the skin, often all three together, and it may be noted that in none of the 20 recorded patients has there been any skin lesion. With all gross brain disorders epilepsy is frequent but, on the available evidence, one affected person had a single fit, and one developed epilepsy at 28, though in three siblings of another affected person death occurred from infantile convulsions. There is, at present, nothing to suggest that this disorder shortens the length of life, nor are we aware of any post-mortem studies.

Summary and Conclusions

An extremely rare hereditary syndrome is described, determined by a single autosomal recessive gene, the incidence of consanguinity in the parents being very high.

The syndrome consists of congenital and stationary cerebellar ataxia, often with evidence of involvement of the pyramidal system; oligophrenia of moderate degree; cataract which appears in childhood and progresses to blindness; multiple minor skeletal anomalies, all the patients being undersized; and in some patients vascular hypertension.

Two new examples are discussed.

We wish to thank Professor C. W. Vining for first calling our attention to the patients described, and to Dr. J. A. Fraser Roberts for his invaluable help and criticism.

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Addendum

Since submitting this paper Professor T. Sjögren has drawn our attention to a report by Gursdorf, Hecaen, and Nau-Massonnet (1952). They describe a girl of 16 suffering from epilepsy and a neurological syndrome, with cerebellar and pyramidal components; she was also mentally backward. This girl, however, was tall and had no cataract. The electro-encephalogram showed changes in keeping with acquired epilepsy. She had had to be revived at birth because of strangulation by the cord and radiographs showed congenital asymmetry of the skull. The mother had had three miscarriages and seven normal pregnancies, and of the latter the patient was the fourth. The second (male, aged 20) had bilateral congenital cataract, a left cerebellar syndrome, was dull and backward, and had had convulsions in infancy. The third (male, aged 18) had congenital cataract, and the fifth (female, age not mentioned) also had congenital cataract and had had infantile convulsions. Further, the mother had congenital cataract and it was known to exist in other members of her family. Whether her marriage was consanguineous is not mentioned.

It will be seen that this family includes a number of abnormal persons amongst whom are found all the components of the syndrome we are discussing, but there is not one affected person showing the complete syndrome and we doubt very much whether it is the same condition; indeed the authors themselves are in some doubt though they appear to incline to the view that this family displays a *forme fruste*. It is unfortunate, for reasons previously mentioned, that they have called this "Sjögren's syndrome", and this is indeed the reason why we overlooked this paper.

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THE RADIOLOGICAL APPEARANCES OF AGENESIS OF THE CORPUS CALLOSUM

BY

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The first case of agenesis of the corpus callosum was reported by Reil in 1812. Eighty-two cases, in which the condition was encountered incidentally at necropsy, were collected from the literature up to 1933 by Baker and Graves.

Despite the introduction of pneumo-encephalography by Dandy in 1918 it was not until 1934 that Davidoff and Dyke established its value in the diagnosis of agenesis of the corpus callosum. In the first of three cases described by these authors the pneumo-encephalogram was interpreted as showing a cyst of the septum pellucidum. However, at necropsy, following a craniotomy, complete agenesis of the corpus callosum was found. The diagnosis is now usually made on the encephalographic findings, and Davidoff and Dyke (1934) enumerate the following diagnostic points: (1) marked separation of the lateral ventricles; (2) angular dorsal margins of the lateral ventricles ("bicornuate" appearance of Hyndman and Penfield, 1937); (3) concave medial borders of the lateral ventricles; (4) dilatation of the posterior horns of the lateral ventricles; (5) enlargement of the interventricular foramina; (6) dorsal extension and dilatation of the third ventricle; (7) a radial arrangement of the medial cerebral sulci around the roof of the third ventricle and extension of these sulci through the zones normally occupied by the corpus callosum.

In 1937 Hyndman and Penfield reported a series of five cases in which pneumo-encephalograms had been performed, and confirmed the importance of the above criteria. They consider that the bicornuate appearance of the lateral ventricles, together with the raised roof of the third ventricle, are diagnostic, but Bunts and Chaffee (1944) in a review of the encephalographic appearances of all published cases, find that while the third ventricle is always raised, the bicornuate shape is not constant.

Hyndman and Penfield also describe the appearances which they consider to be due to partial agenesis and which they call "fish-tailing" of the posterior part of the third ventricle. It may be doubted, however, whether this is anything more than enlargement of the suprapineal recess of the third ventricle (Robertson, 1946) and is thus quite independent of the condition of the corpus callosum itself (Fig. 1). If, however, it is indicative of partial agenesis this condition must be much more common than is suspected, since the appearance is found fairly frequently by chance in otherwise normal ventriculograms and encephalograms.

Since then over 20 cases have been reported in

FIG. 1.—Erect lateral film of an encephalogram on a patient with a temporal lobe abscess.

A chance finding was the very large suprapineal recess which reaches up between the lateral ventricles. (Part of the third ventricle is covered by a burr-hole and the abscess cavity contains thorotrast.)

which the diagnosis has been based on pneumo-encephalographic criteria.

The appearances seen in carotid angiograms in this condition have not previously been reported. In the two cases presented the angiograms showed signs which are probably diagnostic. The position and course of the anterior cerebral artery were unusual and reflected the absence of the corpus callosum. The ascending part of the anterior cerebral artery ran almost directly upwards (Fig. 2a) and then the artery bent sharply backwards. This occurred at a much lower level than in a normal case, and the curve as the artery turned round the genu was absent. The remainder of the course of the pericallosal artery lay immediately above the roof of the third ventricle (Fig. 4). This was in contrast to the normal condition in which the pericallosal artery lies above the corpus callosum and is about 2 cm. superior to the roof of the third ventricle.

The internal cerebral vein lay higher than usual and was also above the roof of the third ventricle. The normal curve of the great cerebral vein was greatly diminished and was situated above and in front of its usual position (Fig. 2c).

In one case the anterior cerebral artery followed a very irregular, wavy course in the antero-posterior views, possibly due to absence of " splinting " by the corpus callosum, but it did not cross the midline (Fig. 2b). In the second case the artery ran a much straighter course in the antero-posterior view

Case Histories

Case 1 (R.I.85311).—This patient, a man aged 28, was admitted to the Radcliffe Infirmary in August, 1950, with a history of fits since the age of 10. They were preceded by an unpleasant sinking feeling in the epigastrium. This was followed by a twitching in the left arm and left leg for about one minute. In the past he had had occasional attacks involving the right side of the body. No loss of consciousness occurred and he understood what people were saying during an attack, though he was unable to speak until it had ended. He had been given anticonvulsant drugs since a few months after the onset of the first fit.

There was nothing relevant in the past personal or family history.

Clinical examination revealed a fit looking, well grown, selfconscious young man. He appeared mentally normal at interview, and psychometric tests revealed no definite impairment, though he seemed to lack any real ambitions and interest in life, and appeared to be very dependent on his parents. The central nervous system was normal, apart from some astereognosis of the left hand. No other clinical abnormality was present.

Straight radiographs of the skull were normal. Examinaton of the cerebrospinal fluid showed it to be under normal pressure, with a protein content of 150 mg./100 ml. and a Lange curve of 1122111100. The serum and cerebrospinal fluid Wassermann and Kahn reactions were negative. The electro-encephalogram showed a precisely localized spike focus in the right precentral region, with an anterior bilateral dysrhythmia.

A lumbar air encephalogram (Figs. 3a and b) showed the points described by Davidoff and Dyke (1934) apart from the radiate arrangement of the medial sulci, which were not examined. The inner borders and the bodies of the lateral ventricles were concave and greatly separated, and the superolateral angles were pointed. There was marked enlargement of the posterior portion of the bodies and posterior horns.

The third ventricle was dilated and its roof was raised to a level only 1 cm. below that of the superolateral margins of the lateral ventricles. The floor, antero-inferior recesses, and anterior wall looked normal (Figs. 3a and b). The region of the pineal body was not well shown, and thus the relationship of the suprapineal recess to the great cerebral vein could not be demonstrated. The foramina of Monro were very large.

In view of the high cerebrospinal fluid protein, the possibility of a neoplasm, for example, lipoma or meningioma, associated with an agenesis was considered, and ventriculograms were therefore also done. However they showed no evidence of a space-occupying lesion.

A right percutaneous common carotid angiogram performed by Dr. Ingmar Wickbom showed that the anterior cerebral and pericallosal arteries ran a very irregular and wavy course. The normally well marked curve of the pericallosal artery passing round the genu of the corpus callosum was absent and was replaced by a sharp kink as the artery turned posteriorly (Fig. 2a). The horizontal portion was low, and was shown to lie immediately above the roof of the third ventricle (Fig. 4). In the antero-posterior arteriogram the anterior cerebral and pericallosal arteries ran a very irregular, loose course always in or just to the right of the midline (Fig. 2b).

The internal and great cerebral veins were shown well in the first and second phlebograms (taken four and eight seconds after the beginning of the injection of 10 ml. of 35% solution of diodone). These were very high in position. The curve of the great cerebral vein, usually caused by passing round the splenium of the corpus callosum, was greatly diminished so that the vein was shortened in the infero-posterior direction. The origin of the straight sinus was not accurately visualized (Fig. 2c).

Other vessels appeared normal in all phases.

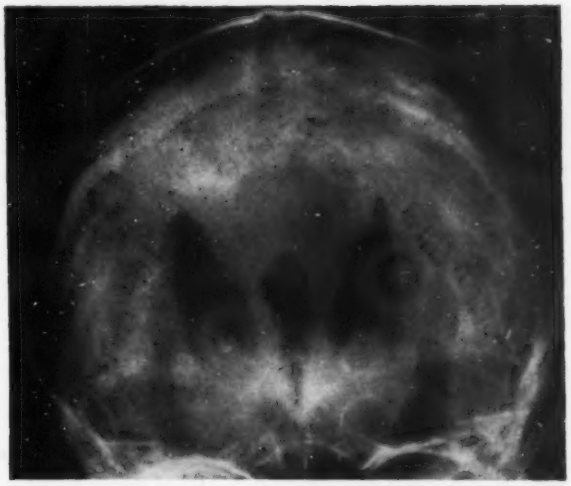
Case 2.—This patient, E. B., a man aged 24, was first seen in December, 1950. He gave a five-month history of repeated focal motor cerebral seizures involving the left side of the body. The attacks were always followed by a very transient weakness and numbness involving the left side of the body. He was otherwise symptom-free apart from occasional headaches.

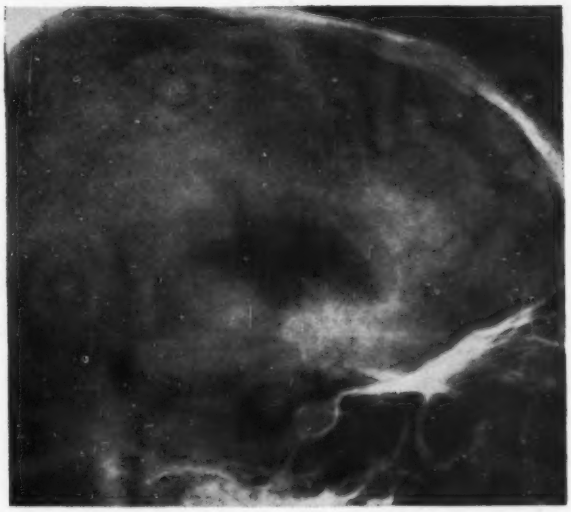
There was nothing relevant in the past personal or family history.

FIG. 2a.—Case 1 : lateral arteriogram. The anterior cerebral artery runs straight up and then turns sharply posteriorly instead of curving smoothly round the genu of the corpus callosum.

FIG. 2b.—Case 1 : A. P. arteriogram showing the wavy, " wandering " course of the anterior cerebral and pericallosal arteries.

FIG. 2c.—Case 1 : lateral phlebogram showing lack of curvature and high position of the internal and great cerebral veins.





FIGS. 3a and b.—Case 1 : A. P. and lateral views of encephalogram. The roof of the third ventricle is considerably raised and lies between the bodies of the lateral ventricles, which are widely separated. The outer angles of lateral ventricles are angulated.

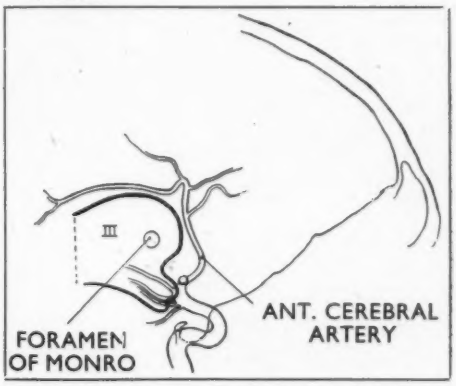


FIG. 4.—Case 1 : a composite drawing showing the relationship of the anterior cerebral and pericallosal arteries to the roof of the third ventricle.

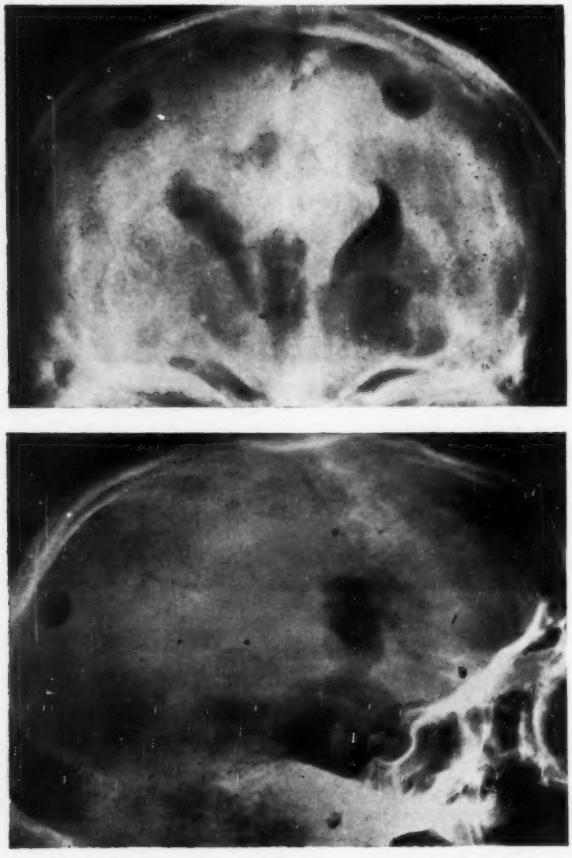
Examination of the central nervous system revealed no abnormality apart from minimal pyramidal signs in the left upper and lower limbs in the form of increased tendon reflexes. There was no evidence of any mental impairment. No other clinical abnormality was detected.

Straight radiographs of the skull were normal. The serum and cerebrospinal fluid Wassermann reactions were negative. The cerebrospinal fluid was under normal pressure with a normal protein content.

An electro-encephalographic tracing showed a good deal of generalized theta activity which was most persistent in the right temporal region and was increased by hypernoea.

A right internal carotid angiogram showed appearances mainly similar to those reported in the previous case. There was, however, one difference, in that the anterior cerebral and pericallosal arteries ran a much straighter course in the antero-posterior arteriograms. (The lateral films have been lost and cannot be reproduced.)

An air encephalogram subsequently carried out showed marked dilatation and upward extension of the third ventricle, which looked normal in its lower part (Figs. 5a and b). The lateral ventricles were thrust apart from above, the medial surfaces were concave, the superomedial angles pointed, more so on the left side (Fig. 5a), and the bodies were dilated posteriorly.



FIGS. 5a and b.—Case 2 : A. P. and lateral films of encephalogram. The angulation of the superolateral margins of the bodies of the lateral ventricles are well marked.

In view of the shape of the lateral ventricles and the high position of the roof of the third ventricle, it was considered that this could only be a case of agenesis of the corpus callosum.

Discussion

Symptomatology.—It is difficult to assess the symptoms of agenesis of the corpus callosum *per se* because the condition is usually associated with other developmental defects of the brain.

From a review of the literature it seems that the most frequent symptoms are epilepsy and a varying degree of mental impairment. The former symptom was present in both the cases reported in this paper, and both showed slight lateralizing signs but no evidence of mental impairment in either case. However, Cameron and Nicholls (1921) and others consider that even total agenesis is possible without any pathognomonic alteration in physical or mental capacity. Bruce (1889), quoting from his own cases and those of others, stated that when the brain is otherwise well developed there may be " no disturbance of mobility, co-ordination, general or specific sensibility, reflexes, speech, or intelligence ". Moreover, Dandy (1931) and others have divided the whole of the corpus callosum in the sagittal plain at operation, and have noted no untoward sequelae.

In the rare cases where the agenesis is accompanied by a tumour of the corpus callosum symptoms are usually present, but these depend on the size and position of the tumour and are not referable to the defect.

Agenesis of the corpus callosum may be associated with extracranial anomalies, such as cleft palate, hare lip, thoracic stomach, and cryptorchidism, but no such abnormalities were found in the cases reported.

Embryology.—The embryology of the corpus callosum and associated structures is of importance in explaining the radiological appearances of agenesis. For this reason it is described at length.

The corpus callosum first appears in the third month of intra-uterine life as a thickening of the lamina terminalis, lying on the dorsal aspect of the hippocampal commissure. The anterior part develops first, and while the initial fibres lie within the limits of the lamina terminalis the corpus callosum gradually increases in size by extending in a cephalic, dorsal, and then caudal direction beyond these limits to form the rostrum and genu. While this is occurring part of the nearby cortex on the medial

surface of both cerebral vesicles is cut off by the developing corpus callosum to form the two leaves of the septum pellucidum.

The body of the corpus callosum continues to grow caudally, carrying with it on its under surface the septum pellucidum and the hippocampal commissure. The commissures come to lie in the midline between the two parts of the body of the fornix. The latter is really a paired structure and the position of the hippocampal commissure assists in its fusion. Thus a single midline structure is formed which acts as an additional roof to the third ventricle, the true roof of which is the original epithelial covering of the neural tube. At the same time the corpus callosum invades the upper part of the hippocampal formation, which becomes thinned out on its surface to form the induseum griseum.

Development is not complete until the fifth month. Agenesis may be complete or partial. Partial agenesis, depending on the state at which arrest takes place (Bruce, 1889) varies all the way from the development of only a rudimentary bundle of fibres to a structure which is almost complete, except for a defect in the splenium (Hyndman and Penfield, 1937).

As the corpus callosum extends backwards, the arrangement of the sulci on the medial surface of the cerebral hemisphere changes from the foetal radiate pattern to the normal adult one. In cases of agenesis the radiate pattern persists.

Abnormalities which are found with agenesis of the corpus callosum may be divided into two groups :—

(1) *Directly Consequent upon Under-development of the Corpus Callosum.*—Under-development of the hippocampal commissures and lack of fusion of the crura of the fornix to form the body of the fornix, with consequent elevation of the third ventricle ; dilatation of the posterior part of the bodies and of the posterior horns of the lateral ventricles ; radiate arrangements of the medial sulci ; absence of the septum pellucidum in cases of complete agenesis.

(2) *Due to Under-development of the Brain in General.*—Polygyria, agyria, microgyria, and pachygyria ; absence of the olfactory nerves ; incomplete separation of the frontal lobes ; microcephaly ; porencephaly.

Occasionally agenesis may be accompanied by a lipoma of the corpus callosum or a meningioma. Such new growths filling the defect or replacing part of the corpus callosum are likely to arise from developmental disturbances in the meninges. Thus occasionally even a typical meningioma may arise at the place of defect. The aetiology of this condition is unknown as is that of many other congenital anomalies.

Differential Diagnosis.—If the radiological appearances of agenesis of the corpus callosum are kept in mind it is unlikely that the abnormality will be missed.

In both the cases reported in the present paper all the criteria of Davidoff and Dyke (1934) were found, with the exception of the radiate pattern of the medial cerebral sulci. Other conditions which may cause confusion are symmetrical tumours of the corpus callosum, notably lipomata, and secondly, cysts and symmetrical tumours of the septum pellucidum.

The most important evidence of a lipoma of the corpus callosum is an area of translucency surrounded by a zone of calcification, situated in the region of the genu, which may be seen on preliminary radiographs of the skull (Sosman, 1946 ; Sutton, 1949). A lipoma is very frequently accompanied by agenesis. Under such circumstances there will be the usual encephalographic signs of agenesis, but the roof of the third ventricle will not be raised as much as usual and will be flattened. The radiological appearances of a lipoma of the corpus callosum without agenesis were described by Mullen and Hannan (1950). The encephalogram showed that the lateral ventricles were dilated, the anterior horns separated by a midline tumour, and the medial borders were concave. The third ventricle was enlarged but the roof was not raised.

Other symmetrical tumours of the corpus callosum are rare. They may cause some concavity of the superior and medial surfaces of the bodies of the lateral ventricles, and possibly angulation of the supero-lateral margins, but the third ventricle will not be raised in position.

Cysts of the septum pellucidum may or may not communicate with the lateral ventricles. A communicating cyst may superficially resemble agenesis of the corpus callosum if the third ventricle is confused with the air-filled cavum septi pellucidi, but in such a case there will be no suggestion of a bicornuate appearance of the lateral ventricles.

Non-communicating cysts cause widening of the septum pellucidum, 3 mm. probably being the upper limit of normal width (Echternacht and Campbell, 1946). The third ventricle is not raised in position, and hydrocephalus may be caused by pressure on the foramina of Monro. While this condition may be confused with a tumour of the corpus callosum or septum pellucidum, it does not resemble agenesis of the corpus callosum.

Agenesis of the corpus callosum should be easily differentiated from above mentioned conditions, provided the position of the third ventricle is well shown.

Symmetrical tumours of the septum pellucidum are also rare. Figs. 6a and b show the appearances of the ventricles found with a longstanding calcified tumour of the septum pellucidum. The nature of this tumour was unverified but was believed to be an oligodendroglioma. In this case the bodies of the lateral ventricles were separated by a midline tumour, which caused a concave filling defect of the medial borders. The superior borders, however, were distended from within, and the supero-lateral margins were rounded in contrast to the angulated appearance found with agenesis of the corpus callosum. Most important was the lack of filling of the upper part of the third ventricle due to pressure on the roof by downward extension of the tumour. Percutaneous carotid angiography (Fig. 6c) showed the pericallosal artery to be raised and stretched and the anterior part to be rounded, in contra-distinction to the appearances seen with agenesis of the corpus callosum. This was partly due to a slight degree of hydrocephalus and possibly partly to extension of the tumour into the corpus callosum. There was no lateral displacement. In addition a pathological circulation could be seen on the phlebograms.

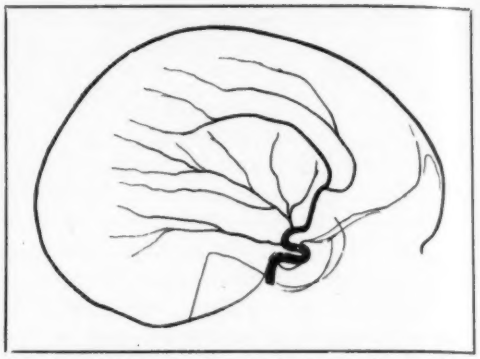
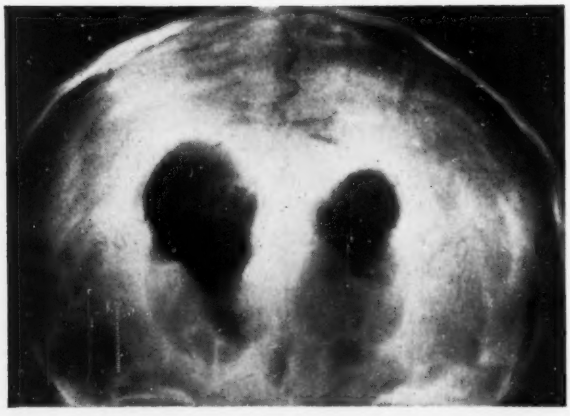
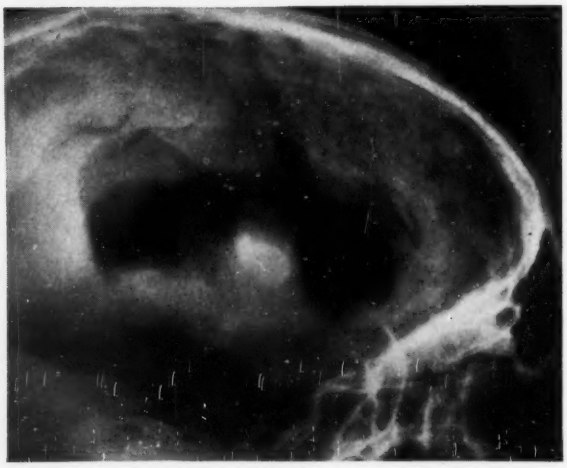


FIG. 6c.—Tracing of a lateral arteriogram showing how the anterior cerebral artery and pericallosal arteries run a rounded, stretched course in the midline.





FIGS. 6a and b.—A. P. and lateral films of ventriculogram of a case of oligodendroglioma of the septum pellucidum showing widening of the septum pellucidum.

The bodies of the lateral ventricles are separated by a midline space-occupying lesion.

The outer angles of lateral ventricles are not angulated as in agenesis of the corpus callosum. The upper part of the third ventricle is considerably depressed.

Use of Angiography in Differential Diagnosis.—The study of these two cases indicates that angiography should be of help in doubtful cases. Apart from the changed position and direction of the midline arteries, one of the most notable findings in these cases of agenesis of the corpus callosum has been the "wandering," irregular character of the courses of these vessels contrasting with the tight stretching and deviation found in cases in which arteries lie close to tumours (Wickbom, 1948). The pericallosal artery runs a normal course in the case of a cyst of the septum pellucidum, but where there is an infiltrating tumour of the corpus callosum the artery is usually displaced and stretched upward and laterally.

No report of the angiographic findings in a case with a lipoma has so far been published. It may be doubted whether the appearances will conform to those seen with an infiltrating tumour of the corpus callosum since operation, and post-mortem studies in the former type of tumour show that the anterior cerebral arteries are actually embedded deep in the tumour and are not displaced.

Summary

Two cases of agenesis of the corpus callosum are reported.

The diagnoses were based on the findings fol-

lowing air encephalography. Carotid angiography was also performed, and it is considered that this method of investigation is of value in diagnosis.

We wish to thank Dr. W. Ritchie Russell for permission to report these two cases, and also Drs. F. H. Kemp, C. W. M. Whitty and Dr. D. M. Richardson for their invaluable help. We are also grateful to Miss Audrey Arnott for the drawings contained in Figs. 4 and 6c.

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THE FEBRUARY (1953) ISSUE

The February (1953) issue contains the following papers :—

Aphasia. By Sir Charles Symonds.

The Effects of Methedrine and of Lysergic Acid Diethylamide on Mental Processes and on the Blood Adrenaline Level. By D. W. Liddell and H. Weil-Malherbe.

Investigation of Amnesic Defects by Progressive Prompting. By Moyra Williams.

The Paraesthesiae Induced by Cold. By John Marshall.

Affective Epilepsy. By L. van der Horst.

The Epileptic Threshold in Schizophrenia. By J. Hoenig and D. M. Leiberman.

Disturbances of Oculomotor Function Accompanying Extradural Haemorrhage. By S. Sunderland and K. C. Bradley.

The Intra-arterial Injection of Neostigmine as a Diagnostic Test in Myasthenia Gravis. By E. C. Hutchinson and W. B. Matthews.

The Neurological Aspects of Dermatomyositis. By W. B. Matthews and J. C. Burne.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

BOOK REVIEWS

Anatomy of the Autonomic Nervous System. By G. A. G. Mitchell, with Foreword by Sir James Learmonth. (Pp. 356 ; 131 figures. 55*s*.) Edinburgh : E. & S. Livingstone. 1953.

This book has many excellent features. It deals with the anatomy of the autonomic system in man from its highest representation in the cortex down to the periphery in viscera and vessels. This in itself makes it unique in the literature of the subject published in this country. The author's personal experience in many of the problems concerned gives it an authenticity often lacking in a textbook. Moreover Professor Mitchell has no hesitation in calling on relevant material from the physiological and clinical fields to support his arguments, and thus adds depth and perspective to the work. It is beautifully produced ; the printing and paper are of pre-war luxuriance. The illustrations, including the photomicrographs, call for special commendation. Full references are given both to classical and contemporary literature. It is likely to become a standard reference work, and will certainly prove of value on many occasions to practising neurologists, as well as those engaged in the " institutes of medicine ". All those concerned are to be congratulated on this production.

The Neurophysiological Basis of Mind : The Principles of Neurophysiology. By J. C. Eccles. (Pp. 314 ; 89 figures. 25*s*.) Oxford University Press (London : Geoffrey Cumberlege). 1953.

This book contains an expanded version of the Wayneflete Lectures given at Oxford in 1952. Most readers will probably consider the subsidiary title more accurate than the main one, for it is not until the last lecture that the relation of mind and brain is developed at all fully, although passing reference is made to the general problem in earlier lectures when the nervous system's function in transmitting and storing information is considered. Nevertheless, the intimate neurophysiology of the neuron must be an important part of the brain-mind inter-relation, as the author emphasizes : and in this sense, the earlier chapters do lead up to the final one even though much of this could have been written without reference to them. An exposition of the modern principles of neurophysiology—perhaps electrophysiology would be more accurate—by an acknowledged authority on the subject will be widely welcomed, and as the book deals with the fundamental background of the subject rather than with an assemblage of related but segregated pieces of research, it fills a very noticeable lacuna in the literature.

In his preface the author suggests that a re-examination of the problems of Cartesian dualism has become profitable in the light of recent neurophysiological advances. This may be so, but the problem of how mind " influences " brain, seems to remain at the end of the book as stubbornly insoluble as it did for Descartes or Sherrington.

Professor Eccles delivered these lectures to crowded audiences, of which physiologists, biochemists, clinicians, general biologists, psychologists, and philosophers, all formed part. The book will have just as wide an appeal, though its main readers will probably be those preparing for an honours degree in physiology, for whom it will be a *sine qua non*.

Different Forms of Signalling Employed by the Nervous System. (University College, London, Inaugural Lecture.) By Berhard Katz. (Pp. 18. 4*s*.) London : H. K. Lewis. 1952.

Those neurologists who rely on someone like Professor Katz to translate into simple language the discoveries of the neurophysiologist will appreciate this lecture. It gives an easily understood account of much of what is known about conduction in both the peripheral nerve and in the central nervous system.

Clinical Neurology. By Frank A. Elliott, Brodie Hughes, and J. W. Aldren Turner. (Pp. 751 ; 8 plates, 22 figures. 42*s*.) London : Cassell & Co. 1953.

It is probably desirable that a new textbook in most medical subjects should be produced every five or 10 years, for authors or those who later edit their texts, find increasing difficulty in representing, by revision or new editions, the changed climate of opinion that pervades any growing clinical subject in a decade or so. This book is therefore welcome and will fulfill a useful purpose. It is significant of the changes that have occurred recently in neurology that a surgical neurologist should be one of the joint authors.

The book is divided into two main sections. In the first and shorter, general points, such as the anatomical and physiological background and methods of examination, are considered. It is a welcome addition to the usual texts to find a chapter here devoted to syndromes characterized by pain. Painful states form a large part of any neurological practice, and it is in conformity with

present trends both of investigation and treatment that they could be grouped together as is done here. The second section is concerned with systematic neurology. Here the usual forms of neurological disease are adequately covered, though the rationale of classification is not always clear. Thus a chapter on demyelinating disease includes disseminated sclerosis while Parkinsonism, motorneuron disease, and rheumatic chorea are under a special heading of diseases of uncertain nature. The book is well produced, and has adequate introductory references and a good index. It will be of value to students in their later clinical years and to practitioners as a source of up-to-date information on current neurological practice.

Poliomyelitis. By W. Ritchie Russell. (Pp. 84 ; 14*s.*) London : Edward Arnold. 1952

This short monograph deals only with certain aspects of anterior poliomyelitis. The author says little about the methods of spread or the morbid anatomy of the disease and concentrates on the more clinical aspects. The account of the natural history of the disease is most readable and the division into " minor " and " major " illnesses valuable, although when more is discovered about the actual events in the nervous system better terms for the various phases of the illness might be devised. The increasingly important question of differential diagnosis in the early stages might with advantage be discussed in greater detail in the next edition. The most valuable part of the book is the full account of the methods of management of the patient ; this section will be of the greatest practical value to all those, whether nurses or doctors, who have to treat patients suffering from poliomyelitis. The author has thought deeply about methods of treatment of bulbar palsy and the use of breathing machines in respiratory paralysis, and if careful attention is given to the methods described lives should be saved. It is interesting to find the author, whose pioneer work on the importance of complete rest in the early stages of the illness is well known, advocating very active exercises within two to three weeks of the acute illness and stating that " physiological fatigue of weak muscles should provide the best natural stimulus to hypertrophy ", but the case he makes for this method of treatment is convincing and if further work confirms this view, Ritchie Russell will have made two valuable contributions to the treatment of poliomyelitis, based on clinical observation. This essentially practical book should be read by any doctor who is likely to see cases of the disease, and if the principles so plainly described are acted upon, his patients will benefit.

Commotio Cerebri : Cerebral Concussion and the Postconcussion Syndrome in their Medical and Legal Aspects. By Cyril B. Courville. (Pp. 161 ; 12 figures. $5.25.) Los Angeles : San Lucas Press. 1953.

Dr. Courville's name is well known to those who study head injuries, and this small monograph will be read closely by many. After interesting chapters on the history of the subject there are some closely reasoned and authoritative sections on the mechanism of concussion, the vascular reaction to concussion, and on the author's special contribution to the subject—the cellular pathology of *commotio cerebri*. Apart from a somewhat unconvincing attempt to distinguish concussion from contusion, the book to this stage is both stimulating and instructive. The later clinical chapters are, however, less inspiring, and the insistence on rest as the keystone of all treatment will surprise British neurologists who discarded prolonged rest as a desirable method of treatment during the late war, and adopted progressive physical exercises as the best means of removing symptoms and preventing the development of psychoneurosis. However, notwithstanding these few comments, neurologists interested in head injuries will like to have this beautifully produced book in their library.

The Biology of Mental Health and Disease. 108 contributors, with Foreword by Stanley Cobb. (Pp. 624 + index ; 213 text figures, 58 tables. 75*s.*) London : Cassell & Co. 1952.

This symposium contains an enormous amount of recent factual information about many aspects of cerebral function. The emphasis is on the preclinical sciences, and biochemical and physiological contributors are prominent. This is in keeping with the recent tendency for psychiatric research to call more on workers in these fields, as investigation on the psychological side seems more difficult and less profitable. The result is a book which will be a valuable source of reference to neurologists, psychiatrists, and many working in related fields. Reading some sections of the book, especially on biochemical and pharmacological aspects, will inevitably suggest direct implications for therapeutic trials, in both psychiatric and neurological disease. It is very desirable that treatment in this field should be based on rational premises, and it is one of the values of this work that it will supply a basis of fact for clinical thought and experiment.

Current Trends in British Psychology. Edited by C. A. Mace and Philip Vernon. (Pp. viii + 262 ; 21 line drawings and 3 plates. 15*s.*) London : Methuen & Co. 1953.

This volume comprises 20 papers read before the Psychology Section of the British Association at Edinburgh in 1951. It falls into two equal parts : in the first, some applications of psychology to problems in industry, personnel selection, education and medicine are considered. In the second, concepts and methods in present-day psychological research are outlined. The distinction is not, however, sharp and in some cases allocation of a paper to one or other part appears distinctly arbitrary. Although much of the work discussed is somewhat pedestrian, this book does serve to give a picture of what British psychologists are doing and the major fields covered by their investigations.

The borderlands of medicine are represented by four papers. Trends in clinical psychology are reviewed by Miss M. A. Davidson, objective psychological studies in

psychiatry by Dr. S. Crown, and psychological research in the field of neurology by Professor O. L. Zangwill. In addition, Dr. J. D. Sutherland contributes a provocative essay on scientific tasks for the psychological clinic. Although these papers solve no major problems, they at least testify to the growth of fruitful collaborative study in the clinical field.

The only paper to offer a real theoretical challenge is Professor R. C. Oldfield's essay on "The Place of Experiment in Psychology". If, as this book suggests, the modern trend in the subject is to apply on an ever-wider scale what is already known, it is reassuring to learn that there is one British psychologist, at least, who cares about finding out something new. As so little is known in psychology anyway, it may be hoped that Professor Oldfield's paper will be closely studied by all who believe in fundamental science.

A Further Study of Visual Perception. By M. D. Vernon. (Pp. 263; 30 figures. 35*s*.) London: Cambridge University Press. 1952.

This work contains a detailed, comprehensive, and up-to-date review of the psychological experiments on visual perception. The author has considered a variety of approaches, and although her final conclusions regarding the nature of perception are not very different from those put forward by Bartlett in 1932, the more recent work has enabled her to clarify the concept of schematization which Bartlett took over from Head. The author has concentrated on systematizing the psychological aspects of perceiving. She does not herself attempt to connect these with physiological processes. Indeed, in the final chapter she suggests that something other than a purely experimental approach to the psychological data will be necessary before the connexions between psychological and physiological mechanisms can be understood.

Social Psychiatry. A Study of Therapeutic Communities. By Maxwell Jones, with Foreword by Prof. Aubrey Lewis. (Pp. 186, + index. 18*s*.) London: Routledge and Kegan Paul. 1952.

The author describes the development of the Industrial Neurosis Unit at Belmont Hospital from earlier experiments of a similar kind. At this Unit patients are treated who have been incapacitated for work by neurotic symptoms, often of prolonged duration. Nevertheless about 44% of men make a satisfactory adjustment to work after discharge. The main mode of treatment is social and psychological, and involves getting the patient to participate actively and productively in the hospital community as a step to social participation in the world outside.

The most interesting section of the book, contributed by Joseph Sandler, relates to the statistical analysis of follow-up data. Many factors which one might have expected to have a prognostic value prove not to be significantly related with the degree of adjustment after discharge. This applies to age on admission, length of stay, wage level, skill, education, amount of unemployment, delinquency record, intelligence. Factors which did have a significant relation with after-history included marital status, amount of previous psychiatric treatment, diagnosis and other types of temperamental assessment, and recorded behaviour while actually in the hospital. Some suggestive comments are made about what is meant by "employability" and the ways in which it may be assessed.

Design for a Brain. By W. Ross Ashby. (Pp. 254; over 50 figures. 36*s*.) London: Chapman and Hall. 1952.

This book will be welcomed by those who have so far withheld definite opinions regarding the value of mechanical models of the brain, as it is written for the major part in non-technical language by one who knows what he is trying to explain. But although mathematics are confined to a separate appendix, considerable concentration is still required to follow many of the arguments, even though the principles are illustrated by familiar events such as a cat creeping up on a dying fire.

The author starts by analysing the essentials of animal behaviour, and deduces that the most fundamental characteristic is that of adaptation to environmental changes. Similar activity is demonstrated by the homeostat, a device long known to engineers and used in automatic steering and heating apparatus. The author shows that it can be reproduced by a number of electro-magnetic cells interconnected at random. Such a design bears many more similarities to what is known of the structure of the brain than the much criticized and complex calculating machines.

There are many aspects of mental activity, even some of adaptation, which the author leaves unexplained, but which readers who feel they can profit from model building may themselves be able to find analogies for in the activity of Dr. Ashby's model. Others may remain of the opinion that they are more likely to further knowledge of cerebral activity by direct study of the brain itself and of its functions.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

The Neurophysiological Basis of Mind. The Principles of Neurophysiology. By John Carew Eccles. (Pp. 314; 89 diagrams. 25*s*.) Oxford University Press (London: Geoffrey Cumberlege). 1953.

New Concepts of Hypnosis. By Bernard C. Gindes, with an Introduction by Robert M. Lindner. (Pp. 272. 15*s*.) London: George Allen and Unwin. 1953.

Clinical Neurology. By Frank A. Elliott, Brodie Hughes, and J. W. Aldren Turner: edited by Frank A. Elliott. (Pp. 751; 8 plates, 22 figures. 42*s*.) London: Cassell and Co. 1953.

How to Use a Medical Library. A Guide for Practitioners, Research Workers and Students. By Leslie T. Morton. (Pp. VII + 40 + index. 5*s*.) London: William Heinemann. 1952.